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(54) Title: COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, particularly lung cancer, are disclosed. Illustrative compositions comprise one or more lung tumor polypeptides, immunogenic portions thereof, polynucleotides that encode such polypeptides, antigen presenting cell that expresses such polypeptides, and T cells that are specific for cells expressing such polypeptides. The disclosed compositions are useful, for example, in the diagnosis, prevention and/or treatment of diseases, particularly lung cancer.

COMPOSITIONS AND METHODS FOR THE THERAPY AND DIAGNOSIS OF LUNG CANCER

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to therapy and diagnosis of cancer, such as lung cancer. The invention is more specifically related to polypeptides, comprising at least a portion of a lung tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides are useful in pharmaceutical compositions, *e.g.*, vaccines, and other compositions for the diagnosis and treatment of lung cancer.

BACKGROUND OF THE INVENTION

Field of the Invention

Lung cancer is the primary cause of cancer death among both men and women in the U.S., with an estimated 172,000 new cases being reported in 1994. The five-year survival rate among all lung cancer patients, regardless of the stage of disease at diagnosis, is only 13%. This contrasts with a five-year survival rate of 46% among cases detected while the disease is still localized. However, only 16% of lung cancers are discovered before the disease has spread.

Description of Related Art

Early detection is difficult since clinical symptoms are often not seen until the disease has reached an advanced stage. Currently, diagnosis is aided by the use of chest x-rays, analysis of the type of cells contained in sputum and fiberoptic examination of the bronchial passages. Treatment regimens are determined by the type and stage of the cancer, and include surgery, radiation therapy and/or chemotherapy. In spite of considerable research into therapies for the disease, lung cancer remains difficult to treat.

Accordingly, there remains a need in the art for improved vaccines, treatment methods and diagnostic techniques for lung cancer.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides polynucleotide compositions comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746;

(b) complements of the sequences provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746;

(d) sequences that hybridize to a sequence provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746, under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746;

(f) sequences having at least 90% identity to a sequence of SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746; and

(g) degenerate variants of a sequence provided in SEQ ID NO: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746.

In one preferred embodiment, the polynucleotide compositions of the invention are expressed in at least about 20%, more preferably in at least about 30%, and most preferably in at least about 50% of lung tumors samples tested, at a level that is at least about 2-fold, preferably at least about 5-fold, and most preferably at least about 10-fold higher than that for normal tissues.

The present invention, in another aspect, provides polypeptide compositions comprising an amino acid sequence that is encoded by a polynucleotide sequence described above.

In specific embodiments, the present invention provides polypeptide compositions comprising an amino acid sequence selected from the group consisting of sequences recited in SEQ ID NO: 391, 393, 395, 397, 421, 425-427, 434-439, 584-587, 738, 739, 742 and 745.

In certain preferred embodiments, the polypeptides and/or polynucleotides of the present invention are immunogenic, *i.e.*, they are capable of eliciting an immune response, particularly a humoral and/or cellular immune response, as further described herein.

The present invention further provides fragments, variants and/or derivatives of the disclosed polypeptide and/or polynucleotide sequences, wherein the fragments, variants and/or derivatives preferably have a level of immunogenic activity of at least about 50%, preferably at least about 70% and more preferably at least about 90% of the level of immunogenic activity of a polypeptide sequence set forth in SEQ ID NOs: 391, 393, 395, 397, 421, 425-427, 434-439, 584-587, 738, 739, 742, 745 and/or a polypeptide sequence encoded by a polynucleotide sequence set forth in SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433 440-583, 588-732, 736, 737, 740, 741, 744 and 746.

The present invention further provides polynucleotides that encode a polypeptide described above, expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, the pharmaceutical compositions, *e.g.*, vaccine compositions, are provided for prophylactic or therapeutic applications. Such compositions generally comprise an immunogenic polypeptide or polynucleotide of the invention and an immunostimulant, such as an adjuvant.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a polypeptide of the present invention, or a fragment thereof; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Illustrative antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, pharmaceutical compositions are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins, typically in the form of pharmaceutical compositions, *e.g.*, vaccine compositions, comprising a physiologically acceptable carrier and/or an immunostimulant. The fusions proteins may comprise multiple immunogenic polypeptides or portions/variants thereof, as described herein, and may further comprise one or more polypeptide segments for facilitating the expression, purification and/or immunogenicity of the polypeptide(s).

Within further aspects, the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response in a human patient, comprising administering a pharmaceutical composition described herein. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition as recited above. The patient may be afflicted with lung cancer, in which case the methods provide treatment for the disease, or patient considered at risk for such a disease may be treated prophylactically.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a polypeptide of the present invention, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a polypeptide of the present invention, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polynucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating $CD4^+$ and/or $CD8^+$ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of polypeptide disclosed herein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer, preferably a lung cancer, in a patient comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the

presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a polypeptide of the present invention; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

SEQUENCE IDENTIFIERS

SEQ ID NO: 1 is the determined cDNA sequence for L363C1.cons
SEQ ID NO: 2 is the determined cDNA sequence for L263C2.cons
SEQ ID NO: 3 is the determined cDNA sequence for L263C2c
SEQ ID NO: 4 is the determined cDNA sequence for L263C1.cons
SEQ ID NO: 5 is the determined cDNA sequence for L263C1b
SEQ ID NO: 6 is the determined cDNA sequence for L164C2.cons
SEQ ID NO: 7 is the determined cDNA sequence for L164C1.cons
SEQ ID NO: 8 is the determined cDNA sequence for L366C1a
SEQ ID NO: 9 is the determined cDNA sequence for L260C1.cons

SEQ ID NO: 10 is the determined cDNA sequence for L163C1c
SEQ ID NO: 11 is the determined cDNA sequence for L163C1b
SEQ ID NO: 12 is the determined cDNA sequence for L255C1.cons
SEQ ID NO: 13 is the determined cDNA sequence for L255C1b
SEQ ID NO: 14 is the determined cDNA sequence for L355C1.cons
SEQ ID NO: 15 is the determined cDNA sequence for L366C1.cons
SEQ ID NO: 16 is the determined cDNA sequence for L163C1a
SEQ ID NO: 17 is the determined cDNA sequence for LT86-1
SEQ ID NO: 18 is the determined cDNA sequence for LT86-2
SEQ ID NO: 19 is the determined cDNA sequence for LT86-3
SEQ ID NO: 20 is the determined cDNA sequence for LT86-4
SEQ ID NO: 21 is the determined cDNA sequence for LT86-5
SEQ ID NO: 22 is the determined cDNA sequence for LT86-6
SEQ ID NO: 23 is the determined cDNA sequence for LT86-7
SEQ ID NO: 24 is the determined cDNA sequence for LT86-8
SEQ ID NO: 25 is the determined cDNA sequence for LT86-9
SEQ ID NO: 26 is the determined cDNA sequence for LT86-10
SEQ ID NO: 27 is the determined cDNA sequence for LT86-11
SEQ ID NO: 28 is the determined cDNA sequence for LT86-12
SEQ ID NO: 29 is the determined cDNA sequence for LT86-13
SEQ ID NO: 30 is the determined cDNA sequence for LT86-14
SEQ ID NO: 31 is the determined cDNA sequence for LT86-15
SEQ ID NO: 32 is the predicted amino acid sequence for LT86-1
SEQ ID NO: 33 is the predicted amino acid sequence for LT86-2
SEQ ID NO: 34 is the predicted amino acid sequence for LT86-3
SEQ ID NO: 35 is the predicted amino acid sequence for LT86-4
SEQ ID NO: 36 is the predicted amino acid sequence for LT86-5
SEQ ID NO: 37 is the predicted amino acid sequence for LT86-6
SEQ ID NO: 38 is the predicted amino acid sequence for LT86-7
SEQ ID NO: 39 is the predicted amino acid sequence for LT86-8
SEQ ID NO: 40 is the predicted amino acid sequence for LT86-9
SEQ ID NO: 41 is the predicted amino acid sequence for LT86-10
SEQ ID NO: 42 is the predicted amino acid sequence for LT86-11
SEQ ID NO: 43 is the predicted amino acid sequence for LT86-12
SEQ ID NO: 44 is the predicted amino acid sequence for LT86-13
SEQ ID NO: 45 is the predicted amino acid sequence for LT86-14

SEQ ID NO: 46 is the predicted amino acid sequence for LT86-15
SEQ ID NO: 47 is a $(dT)_{12}AG$ primer
SEQ ID NO: 48 is a primer
SEQ ID NO: 49 is the determined 5' cDNA sequence for L86S-3
SEQ ID NO: 50 is the determined 5' cDNA sequence for L86S-12
SEQ ID NO: 51 is the determined 5' cDNA sequence for L86S-16
SEQ ID NO: 52 is the determined 5' cDNA sequence for L86S-25
SEQ ID NO: 53 is the determined 5' cDNA sequence for L86S-36
SEQ ID NO: 54 is the determined 5' cDNA sequence for L86S-40
SEQ ID NO: 55 is the determined 5' cDNA sequence for L86S-46
SEQ ID NO: 56 is the predicted amino acid sequence for L86S-3
SEQ ID NO: 57 is the predicted amino acid sequence for L86S-12
SEQ ID NO: 58 is the predicted amino acid sequence for L86S-16
SEQ ID NO: 59 is the predicted amino acid sequence for L86S-25
SEQ ID NO: 60 is the predicted amino acid sequence for L86S-36
SEQ ID NO: 61 is the predicted amino acid sequence for L86S-40
SEQ ID NO: 62 is the predicted amino acid sequence for L86S-46
SEQ ID NO: 63 is the determined 5' cDNA sequence for L86S-30
SEQ ID NO: 64 is the determined 5' cDNA sequence for L86S-41
SEQ ID NO: 65 is the predicted amino acid sequence from the 5' end of LT86-9
SEQ ID NO: 66 is the determined extended cDNA sequence for LT86-4
SEQ ID NO: 67 is the predicted extended amino acid sequence for LT86-4
SEQ ID NO: 68 is the determined 5' cDNA sequence for LT86-20
SEQ ID NO: 69 is the determined 3' cDNA sequence for LT86-21
SEQ ID NO: 70 is the determined 5' cDNA sequence for LT86-22
SEQ ID NO: 71 is the determined 5' cDNA sequence for LT86-26
SEQ ID NO: 72 is the determined 5' cDNA sequence for LT86-27
SEQ ID NO: 73 is the predicted amino acid sequence for LT86-20
SEQ ID NO: 74 is the predicted amino acid sequence for LT86-21
SEQ ID NO: 75 is the predicted amino acid sequence for LT86-22
SEQ ID NO: 76 is the predicted amino acid sequence for LT86-26
SEQ ID NO: 77 is the predicted amino acid sequence for LT86-27
SEQ ID NO: 78 is the determined extended cDNA sequence for L86S-12
SEQ ID NO: 79 is the determined extended cDNA sequence for L86S-36

SEQ ID NO: 80 is the determined extended cDNA sequence for L86S-46
SEQ ID NO: 81 is the predicted extended amino acid sequence for L86S-12
SEQ ID NO: 82 is the predicted extended amino acid sequence for L86S-36
SEQ ID NO: 83 is the predicted extended amino acid sequence for L86S-46
SEQ ID NO: 84 is the determined 5'cDNA sequence for L86S-6
SEQ ID NO: 85 is the determined 5'cDNA sequence for L86S-11
SEQ ID NO: 86 is the determined 5'cDNA sequence for L86S-14
SEQ ID NO: 87 is the determined 5'cDNA sequence for L86S-29
SEQ ID NO: 88 is the determined 5'cDNA sequence for L86S-34
SEQ ID NO: 89 is the determined 5'cDNA sequence for L86S-39
SEQ ID NO: 90 is the determined 5'cDNA sequence for L86S-47
SEQ ID NO: 91 is the determined 5'cDNA sequence for L86S-49
SEQ ID NO: 92 is the determined 5'cDNA sequence for L86S-51
SEQ ID NO: 93 is the predicted amino acid sequence for L86S-6
SEQ ID NO: 94 is the predicted amino acid sequence for L86S-11
SEQ ID NO: 95 is the predicted amino acid sequence for L86S-14
SEQ ID NO: 96 is the predicted amino acid sequence for L86S-29
SEQ ID NO: 97 is the predicted amino acid sequence for L86S-34
SEQ ID NO: 98 is the predicted amino acid sequence for L86S-39
SEQ ID NO: 99 is the predicted amino acid sequence for L86S-47
SEQ ID NO: 100 is the predicted amino acid sequence for L86S-49
SEQ ID NO: 101 is the predicted amino acid sequence for L86S-51
SEQ ID NO: 102 is the determined DNA sequence for SLT-T1
SEQ ID NO: 103 is the determined 5' cDNA sequence for SLT-T2
SEQ ID NO: 104 is the determined 5' cDNA sequence for SLT-T3
SEQ ID NO: 105 is the determined 5' cDNA sequence for SLT-T5
SEQ ID NO: 106 is the determined 5' cDNA sequence for SLT-T7
SEQ ID NO: 107 is the determined 5' cDNA sequence for SLT-T9
SEQ ID NO: 108 is the determined 5' cDNA sequence for SLT-T10
SEQ ID NO: 109 is the determined 5' cDNA sequence for SLT-T11
SEQ ID NO: 110 is the determined 5' cDNA sequence for SLT-T12
SEQ ID NO: 111 is the predicted amino acid sequence for SLT-T1
SEQ ID NO: 112 is the predicted amino acid sequence for SLT-T2

SEQ ID NO: 113 is the predicted amino acid sequence for SLT-T3
SEQ ID NO: 114 is the predicted amino acid sequence for SLT-T10
SEQ ID NO: 115 is the predicted amino acid sequence for SLT-T12
SEQ ID NO: 116 is the determined 5' cDNA sequence for SALT-T3
SEQ ID NO: 117 is the determined 5' cDNA sequence for SALT-T4
SEQ ID NO: 118 is the determined 5' cDNA sequence for SALT-T7
SEQ ID NO: 119 is the determined 5' cDNA sequence for SALT-T8
SEQ ID NO: 120 is the determined 5' cDNA sequence for SALT-T9
SEQ ID NO: 121 is the predicted amino acid sequence for SALT-T3
SEQ ID NO: 122 is the predicted amino acid sequence for SALT-T4
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SEQ ID NO: 124 is the predicted amino acid sequence for SALT-T8
SEQ ID NO: 125 is the predicted amino acid sequence for SALT-T9
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SEQ ID NO: 127 is the determined cDNA sequence for PSLT-2
SEQ ID NO: 128 is the determined cDNA sequence for PSLT-7
SEQ ID NO: 129 is the determined cDNA sequence for PSLT-13
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SEQ ID NO: 132 is the determined cDNA sequence for PSLT-30
SEQ ID NO: 133 is the determined cDNA sequence for PSLT-40
SEQ ID NO: 134 is the determined cDNA sequence for PSLT-69
SEQ ID NO: 135 is the determined cDNA sequence for PSLT-71
SEQ ID NO: 136 is the determined cDNA sequence for PSLT-73
SEQ ID NO: 137 is the determined cDNA sequence for PSLT-79
SEQ ID NO: 138 is the determined cDNA sequence for PSLT-03
SEQ ID NO: 139 is the determined cDNA sequence for PSLT-09
SEQ ID NO: 140 is the determined cDNA sequence for PSLT-011
SEQ ID NO: 141 is the determined cDNA sequence for PSLT-041
SEQ ID NO: 142 is the determined cDNA sequence for PSLT-62
SEQ ID NO: 143 is the determined cDNA sequence for PSLT-6
SEQ ID NO: 144 is the determined cDNA sequence for PSLT-37
SEQ ID NO: 145 is the determined cDNA sequence for PSLT-74
SEQ ID NO: 146 is the determined cDNA sequence for PSLT-010
SEQ ID NO: 147 is the determined cDNA sequence for PSLT-012
SEQ ID NO: 148 is the determined cDNA sequence for PSLT-037

SEQ ID NO: 149 is the determined 5' cDNA sequence for SAL-3
SEQ ID NO: 150 is the determined 5' cDNA sequence for SAL-24
SEQ ID NO: 151 is the determined 5' cDNA sequence for SAL-25
SEQ ID NO: 152 is the determined 5' cDNA sequence for SAL-33
SEQ ID NO: 153 is the determined 5' cDNA sequence for SAL-50
SEQ ID NO: 154 is the determined 5' cDNA sequence for SAL-57
SEQ ID NO: 155 is the determined 5' cDNA sequence for SAL-66
SEQ ID NO: 156 is the determined 5' cDNA sequence for SAL-82
SEQ ID NO: 157 is the determined 5' cDNA sequence for SAL-99
SEQ ID NO: 158 is the determined 5' cDNA sequence for SAL-104
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SEQ ID NO: 160 is the determined 5' cDNA sequence for SAL-5
SEQ ID NO: 161 is the determined 5' cDNA sequence for SAL-8
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SEQ ID NO: 164 is the determined 5' cDNA sequence for SAL-16
SEQ ID NO: 165 is the determined 5' cDNA sequence for SAL-23
SEQ ID NO: 166 is the determined 5' cDNA sequence for SAL-26
SEQ ID NO: 167 is the determined 5' cDNA sequence for SAL-29
SEQ ID NO: 168 is the determined 5' cDNA sequence for SAL-32
SEQ ID NO: 169 is the determined 5' cDNA sequence for SAL-39
SEQ ID NO: 170 is the determined 5' cDNA sequence for SAL-42
SEQ ID NO: 171 is the determined 5' cDNA sequence for SAL-43
SEQ ID NO: 172 is the determined 5' cDNA sequence for SAL-44
SEQ ID NO: 173 is the determined 5' cDNA sequence for SAL-48
SEQ ID NO: 174 is the determined 5' cDNA sequence for SAL-68
SEQ ID NO: 175 is the determined 5' cDNA sequence for SAL-72
SEQ ID NO: 176 is the determined 5' cDNA sequence for SAL-77
SEQ ID NO: 177 is the determined 5' cDNA sequence for SAL-86
SEQ ID NO: 178 is the determined 5' cDNA sequence for SAL-88
SEQ ID NO: 179 is the determined 5' cDNA sequence for SAL-93
SEQ ID NO: 180 is the determined 5' cDNA sequence for SAL-100
SEQ ID NO: 181 is the determined 5' cDNA sequence for SAL-105
SEQ ID NO: 182 is the predicted amino acid sequence for SAL-3
SEQ ID NO: 183 is the predicted amino acid sequence for SAL-24
SEQ ID NO: 184 is a first predicted amino acid sequence for SAL-25

SEQ ID NO: 185 is a second predicted amino acid sequence for SAL-25
SEQ ID NO: 186 is the predicted amino acid sequence for SAL-33
SEQ ID NO: 187 is a first predicted amino acid sequence for SAL-50
SEQ ID NO: 188 is the predicted amino acid sequence for SAL-57
SEQ ID NO: 189 is a first predicted amino acid sequence for SAL-66
SEQ ID NO: 190 is a second predicted amino acid sequence for SAL-66
SEQ ID NO: 191 is the predicted amino acid sequence for SAL-82
SEQ ID NO: 192 is the predicted amino acid sequence for SAL-99
SEQ ID NO: 193 is the predicted amino acid sequence for SAL-104
SEQ ID NO: 194 is the predicted amino acid sequence for SAL-5
SEQ ID NO: 195 is the predicted amino acid sequence for SAL-8
SEQ ID NO: 196 is the predicted amino acid sequence for SAL-12
SEQ ID NO: 197 is the predicted amino acid sequence for SAL-14
SEQ ID NO: 198 is the predicted amino acid sequence for SAL-16
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SEQ ID NO: 201 is the predicted amino acid sequence for SAL-29
SEQ ID NO: 202 is the predicted amino acid sequence for SAL-32
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SEQ ID NO: 204 is the predicted amino acid sequence for SAL-42
SEQ ID NO: 205 is the predicted amino acid sequence for SAL-43
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SEQ ID NO: 207 is the predicted amino acid sequence for SAL-48
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SEQ ID NO: 210 is the predicted amino acid sequence for SAL-77
SEQ ID NO: 211 is the predicted amino acid sequence for SAL-86
SEQ ID NO: 212 is the predicted amino acid sequence for SAL-88
SEQ ID NO: 213 is the predicted amino acid sequence for SAL-93
SEQ ID NO: 214 is the predicted amino acid sequence for SAL-100
SEQ ID NO: 215 is the predicted amino acid sequence for SAL-105
SEQ ID NO: 216 is a second predicted amino acid sequence for SAL-50
SEQ ID NO: 217 is the determined cDNA sequence for SSLT-4
SEQ ID NO: 218 is the determined cDNA sequence for SSLT-9
SEQ ID NO: 219 is the determined cDNA sequence for SSLT-10
SEQ ID NO: 220 is the determined cDNA sequence for SSLT-12

SEQ ID NO: 221 is the determined cDNA sequence for SSLT-19
SEQ ID NO: 222 is the determined cDNA sequence for SSLT-31
SEQ ID NO: 223 is the determined cDNA sequence for SSLT-38
SEQ ID NO: 224 is the determined cDNA sequence for LT4690-2
SEQ ID NO: 225 is the determined cDNA sequence for LT4690-3
SEQ ID NO: 226 is the determined cDNA sequence for LT4690-22
SEQ ID NO: 227 is the determined cDNA sequence for LT4690-24
SEQ ID NO: 228 is the determined cDNA sequence for LT4690-37
SEQ ID NO: 229 is the determined cDNA sequence for LT4690-39
SEQ ID NO: 230 is the determined cDNA sequence for LT4690-40
SEQ ID NO: 231 is the determined cDNA sequence for LT4690-41
SEQ ID NO: 232 is the determined cDNA sequence for LT4690-49
SEQ ID NO: 233 is the determined 3' cDNA sequence for LT4690-55
SEQ ID NO: 234 is the determined 5' cDNA sequence for LT4690-55
SEQ ID NO: 235 is the determined cDNA sequence for LT4690-59
SEQ ID NO: 236 is the determined cDNA sequence for LT4690-63
SEQ ID NO: 237 is the determined cDNA sequence for LT4690-71
SEQ ID NO: 238 is the determined cDNA sequence for 2LT-3
SEQ ID NO: 239 is the determined cDNA sequence for 2LT-6
SEQ ID NO: 240 is the determined cDNA sequence for 2LT-22
SEQ ID NO: 241 is the determined cDNA sequence for 2LT-25
SEQ ID NO: 242 is the determined cDNA sequence for 2LT-26
SEQ ID NO: 243 is the determined cDNA sequence for 2LT-31
SEQ ID NO: 244 is the determined cDNA sequence for 2LT-36
SEQ ID NO: 245 is the determined cDNA sequence for 2LT-42
SEQ ID NO: 246 is the determined cDNA sequence for 2LT-44
SEQ ID NO: 247 is the determined cDNA sequence for 2LT-54
SEQ ID NO: 248 is the determined cDNA sequence for 2LT-55
SEQ ID NO: 249 is the determined cDNA sequence for 2LT-57
SEQ ID NO: 250 is the determined cDNA sequence for 2LT-58
SEQ ID NO: 251 is the determined cDNA sequence for 2LT-59
SEQ ID NO: 252 is the determined cDNA sequence for 2LT-62
SEQ ID NO: 253 is the determined cDNA sequence for 2LT-63
SEQ ID NO: 254 is the determined cDNA sequence for 2LT-65
SEQ ID NO: 255 is the determined cDNA sequence for 2LT-66
SEQ ID NO: 256 is the determined cDNA sequence for 2LT-70

SEQ ID NO: 257 is the determined cDNA sequence for 2LT-73
SEQ ID NO: 258 is the determined cDNA sequence for 2LT-74
SEQ ID NO: 259 is the determined cDNA sequence for 2LT-76
SEQ ID NO: 260 is the determined cDNA sequence for 2LT-77
SEQ ID NO: 261 is the determined cDNA sequence for 2LT-78
SEQ ID NO: 262 is the determined cDNA sequence for 2LT-80
SEQ ID NO: 263 is the determined cDNA sequence for 2LT-85
SEQ ID NO: 264 is the determined cDNA sequence for 2LT-87
SEQ ID NO: 265 is the determined cDNA sequence for 2LT-89
SEQ ID NO: 266 is the determined cDNA sequence for 2LT-94
SEQ ID NO: 267 is the determined cDNA sequence for 2LT-95
SEQ ID NO: 268 is the determined cDNA sequence for 2LT-98
SEQ ID NO: 269 is the determined cDNA sequence for 2LT-100
SEQ ID NO: 270 is the determined cDNA sequence for 2LT-103
SEQ ID NO: 271 is the determined cDNA sequence for 2LT-105
SEQ ID NO: 272 is the determined cDNA sequence for 2LT-107
SEQ ID NO: 273 is the determined cDNA sequence for 2LT-108
SEQ ID NO: 274 is the determined cDNA sequence for 2LT-109
SEQ ID NO: 275 is the determined cDNA sequence for 2LT-118
SEQ ID NO: 276 is the determined cDNA sequence for 2LT-120
SEQ ID NO: 277 is the determined cDNA sequence for 2LT-121
SEQ ID NO: 278 is the determined cDNA sequence for 2LT-122
SEQ ID NO: 279 is the determined cDNA sequence for 2LT-124
SEQ ID NO: 280 is the determined cDNA sequence for 2LT-126
SEQ ID NO: 281 is the determined cDNA sequence for 2LT-127
SEQ ID NO: 282 is the determined cDNA sequence for 2LT-128
SEQ ID NO: 283 is the determined cDNA sequence for 2LT-129
SEQ ID NO: 284 is the determined cDNA sequence for 2LT-133
SEQ ID NO: 285 is the determined cDNA sequence for 2LT-137
SEQ ID NO: 286 is the determined cDNA sequence for LT4690-71
SEQ ID NO: 287 is the determined cDNA sequence for LT4690-82
SEQ ID NO: 288 is the determined full-length cDNA sequence for SSLT-74
SEQ ID NO: 289 is the determined cDNA sequence for SSLT-78
SEQ ID NO: 290 is the determined cDNA sequence for SCC1-8.
SEQ ID NO: 291 is the determined cDNA sequence for SCC1-12.

SEQ ID NO: 292 is the determined cDNA sequence for SCC1-336
SEQ ID NO: 293 is the determined cDNA sequence for SCC1-344
SEQ ID NO: 294 is the determined cDNA sequence for SCC1-345
SEQ ID NO: 295 is the determined cDNA sequence for SCC1-346
SEQ ID NO: 296 is the determined cDNA sequence for SCC1-348
SEQ ID NO: 297 is the determined cDNA sequence for SCC1-350
SEQ ID NO: 298 is the determined cDNA sequence for SCC1-352
SEQ ID NO: 299 is the determined cDNA sequence for SCC1-354
SEQ ID NO: 300 is the determined cDNA sequence for SCC1-355
SEQ ID NO: 301 is the determined cDNA sequence for SCC1-356
SEQ ID NO: 302 is the determined cDNA sequence for SCC1-357
SEQ ID NO: 303 is the determined cDNA sequence for SCC1-501
SEQ ID NO: 304 is the determined cDNA sequence for SCC1-503
SEQ ID NO: 305 is the determined cDNA sequence for SCC1-513
SEQ ID NO: 306 is the determined cDNA sequence for SCC1-516
SEQ ID NO: 307 is the determined cDNA sequence for SCC1-518
SEQ ID NO: 308 is the determined cDNA sequence for SCC1-519
SEQ ID NO: 309 is the determined cDNA sequence for SCC1-522
SEQ ID NO: 310 is the determined cDNA sequence for SCC1-523
SEQ ID NO: 311 is the determined cDNA sequence for SCC1-525
SEQ ID NO: 312 is the determined cDNA sequence for SCC1-527
SEQ ID NO: 313 is the determined cDNA sequence for SCC1-529
SEQ ID NO: 314 is the determined cDNA sequence for SCC1-530
SEQ ID NO: 315 is the determined cDNA sequence for SCC1-531
SEQ ID NO: 316 is the determined cDNA sequence for SCC1-532
SEQ ID NO: 317 is the determined cDNA sequence for SCC1-533
SEQ ID NO: 318 is the determined cDNA sequence for SCC1-536
SEQ ID NO: 319 is the determined cDNA sequence for SCC1-538
SEQ ID NO: 320 is the determined cDNA sequence for SCC1-539
SEQ ID NO: 321 is the determined cDNA sequence for SCC1-541
SEQ ID NO: 322 is the determined cDNA sequence for SCC1-542
SEQ ID NO: 323 is the determined cDNA sequence for SCC1-546
SEQ ID NO: 324 is the determined cDNA sequence for SCC1-549
SEQ ID NO: 325 is the determined cDNA sequence for SCC1-551
SEQ ID NO: 326 is the determined cDNA sequence for SCC1-552
SEQ ID NO: 327 is the determined cDNA sequence for SCC1-554

SEQ ID NO: 328 is the determined cDNA sequence for SCC1-558
SEQ ID NO: 329 is the determined cDNA sequence for SCC1-559
SEQ ID NO: 330 is the determined cDNA sequence for SCC1-561
SEQ ID NO: 331 is the determined cDNA sequence for SCC1-562
SEQ ID NO: 332 is the determined cDNA sequence for SCC1-564
SEQ ID NO: 333 is the determined cDNA sequence for SCC1-565
SEQ ID NO: 334 is the determined cDNA sequence for SCC1-566
SEQ ID NO: 335 is the determined cDNA sequence for SCC1-567
SEQ ID NO: 336 is the determined cDNA sequence for SCC1-568
SEQ ID NO: 337 is the determined cDNA sequence for SCC1-570
SEQ ID NO: 338 is the determined cDNA sequence for SCC1-572
SEQ ID NO: 339 is the determined cDNA sequence for SCC1-575
SEQ ID NO: 340 is the determined cDNA sequence for SCC1-576
SEQ ID NO: 341 is the determined cDNA sequence for SCC1-577
SEQ ID NO: 342 is the determined cDNA sequence for SCC1-578
SEQ ID NO: 343 is the determined cDNA sequence for SCC1-582
SEQ ID NO: 344 is the determined cDNA sequence for SCC1-583
SEQ ID NO: 345 is the determined cDNA sequence for SCC1-586
SEQ ID NO: 346 is the determined cDNA sequence for SCC1-588
SEQ ID NO: 347 is the determined cDNA sequence for SCC1-590
SEQ ID NO: 348 is the determined cDNA sequence for SCC1-591
SEQ ID NO: 349 is the determined cDNA sequence for SCC1-592
SEQ ID NO: 350 is the determined cDNA sequence for SCC1-593
SEQ ID NO: 351 is the determined cDNA sequence for SCC1-594
SEQ ID NO: 352 is the determined cDNA sequence for SCC1-595
SEQ ID NO: 353 is the determined cDNA sequence for SCC1-596
SEQ ID NO: 354 is the determined cDNA sequence for SCC1-598
SEQ ID NO: 355 is the determined cDNA sequence for SCC1-599
SEQ ID NO: 356 is the determined cDNA sequence for SCC1-602
SEQ ID NO: 357 is the determined cDNA sequence for SCC1-604
SEQ ID NO: 358 is the determined cDNA sequence for SCC1-605
SEQ ID NO: 359 is the determined cDNA sequence for SCC1-606
SEQ ID NO: 360 is the determined cDNA sequence for SCC1-607
SEQ ID NO: 361 is the determined cDNA sequence for SCC1-608
SEQ ID NO: 362 is the determined cDNA sequence for SCC1-610
SEQ ID NO: 363 is the determined cDNA sequence for clone DMS79T1

SEQ ID NO: 364 is the determined cDNA sequence for clone DMS79T2
SEQ ID NO: 365 is the determined cDNA sequence for clone DMS79T3
SEQ ID NO: 366 is the determined cDNA sequence for clone DMS79T5
SEQ ID NO: 367 is the determined cDNA sequence for clone DMS79T6
SEQ ID NO: 368 is the determined cDNA sequence for clone DMS79T7
SEQ ID NO: 369 is the determined cDNA sequence for clone DMS79T9
SEQ ID NO: 370 is the determined cDNA sequence for clone DMS79T10
SEQ ID NO: 371 is the determined cDNA sequence for clone DMS79T11
SEQ ID NO: 372 is the determined cDNA sequence for clone 128T1
SEQ ID NO: 373 is the determined cDNA sequence for clone 128T2
SEQ ID NO: 374 is the determined cDNA sequence for clone 128T3
SEQ ID NO: 375 is the determined cDNA sequence for clone 128T4
SEQ ID NO: 376 is the determined cDNA sequence for clone 128T5
SEQ ID NO: 377 is the determined cDNA sequence for clone 128T7
SEQ ID NO: 378 is the determined cDNA sequence for clone 128T9
SEQ ID NO: 379 is the determined cDNA sequence for clone 128T10
SEQ ID NO: 380 is the determined cDNA sequence for clone 128T11
SEQ ID NO: 381 is the determined cDNA sequence for clone 128T12
SEQ ID NO: 382 is the determined cDNA sequence for clone NCIH69T3
SEQ ID NO: 383 is the determined cDNA sequence for clone NCIH69T5
SEQ ID NO: 384 is the determined cDNA sequence for clone NCIH69T6
SEQ ID NO: 385 is the determined cDNA sequence for clone NCIH69T7
SEQ ID NO: 386 is the determined cDNA sequence for clone NCIH69T9
SEQ ID NO: 387 is the determined cDNA sequence for clone NCIH69T10
SEQ ID NO: 388 is the determined cDNA sequence for clone NCIH69T11
SEQ ID NO: 389 is the determined cDNA sequence for clone NCIH69T12

SEQ ID NO: 390 is the full-length cDNA sequence for 128T1
SEQ ID NO: 391 is the amino acid sequence for 128T1
SEQ ID NO: 392 is the full-length cDNA sequence for 2LT-128
SEQ ID NO: 393 is the amino acid sequence for 2LT-128
SEQ ID NO: 394 is an extended cDNA sequence for clone SCC1-542
SEQ ID NO: 395 is the amino acid sequence corresponding to SEQ ID NO:394
SEQ ID NO: 396 is an extended cDNA sequence for clone SCC1-593
SEQ ID NO: 397 is the amino acid sequence corresponding to SEQ ID NO:396
SEQ ID NO:398 is the determined cDNA sequence for 55508.1
SEQ ID NO:399 is the determined cDNA sequence for 55509.1
SEQ ID NO:400 is the determined cDNA sequence for 54243.1
SEQ ID NO:401 is the determined cDNA sequence for 54251.1
SEQ ID NO:402 is the determined cDNA sequence for 54252.1
SEQ ID NO:403 is the determined cDNA sequence for 54253.1
SEQ ID NO:404 is the determined cDNA sequence for 55518.1
SEQ ID NO:405 is the determined cDNA sequence for 54258.1
SEQ ID NO:406 is the determined cDNA sequence for 54575.1
SEQ ID NO:407 is the determined cDNA sequence for 54577.1
SEQ ID NO:408 is the determined cDNA sequence for 54584.1
SEQ ID NO:409 is the determined cDNA sequence for 55521.1
SEQ ID NO:410 is the determined cDNA sequence for 54589.1
SEQ ID NO:411 is the determined cDNA sequence for 54592.1
SEQ ID NO:412 is the determined cDNA sequence for 55134.1
SEQ ID NO:413 is the determined cDNA sequence for 55137.1
SEQ ID NO:414 is the determined cDNA sequence for 55140.1
SEQ ID NO:415 is the determined cDNA sequence for 55531.1
SEQ ID NO:416 is the determined cDNA sequence for 55532.1
SEQ ID NO:417 is the determined cDNA sequence for 54621.1
SEQ ID NO:418 is the determined cDNA sequence for 55548.1
SEQ ID NO:419 is the determined cDNA sequence for 54623.1
SEQ ID NO:420 is the determined cDNA sequence for L39
SEQ ID NO:421 is the predicted amino acid sequence for L39
SEQ ID NO:422 is the determined cDNA sequence for SCC2-29
SEQ ID NO:423 is the determined cDNA sequence for SCC2-36

SEQ ID NO:424 is the determined cDNA sequence for SCC2-60

SEQ ID NO:425 is the predicted amino acid sequence for SCC2-29

SEQ ID NO:426 is the predicted amino acid sequence for SCC2-36

SEQ ID NO:427 is the predicted amino acid sequence for SCC2-60

SEQ ID NO:428 is an extended cDNA sequence for the clone 20129, also referred to as 2LT-3, set forth in SEQ ID NO: 238

SEQ ID NO:429 is an extended cDNA sequence for the clone 20347, also referred to as 2LT-26, set forth in SEQ ID NO: 242

SEQ ID NO:430 is an extended cDNA sequence for the clone 21282, also referred to as 2LT-57, set forth in SEQ ID NO: 249

SEQ ID NO:431 is an extended cDNA sequence for the clone 21283, also referred to as 2LT-58, set forth in SEQ ID NO: 250

SEQ ID NO:432 is an extended cDNA sequence for the clone 21484, also referred to as 2LT-98, set forth in SEQ ID NO: 268

SEQ ID NO:433 is an extended cDNA sequence for the clone 21871, also referred to as 2LT-124, set forth in SEQ ID NO: 279

SEQ ID NO:434 is an amino acid sequence encoded by SEQ ID NO: 428

SEQ ID NO:435 is an amino acid sequence encoded by SEQ ID NO: 429

SEQ ID NO:436 is an amino acid sequence encoded by SEQ ID NO: 430

SEQ ID NO:437 is an amino acid sequence encoded by SEQ ID NO: 431

SEQ ID NO:438 is an amino acid sequence encoded by SEQ ID NO: 432

SEQ ID NO:439 is an amino acid sequence encoded by SEQ ID NO: 433

SEQ ID NO:440 is the determined cDNA sequence for clone 19A4

SEQ ID NO: 441 is the determined full-length cDNA sequence for clone 14F10.

SEQ ID NO: 442 is the determined 5' cDNA sequence for clone 20E10.

SEQ ID NO: 443 is a first determined cDNA sequence for clone 55153.

SEQ ID NO: 444 is a second determined cDNA sequence for clone 55153.

SEQ ID NO: 445 is a first determined cDNA sequence for clone 55154.

SEQ ID NO: 446 is a second determined cDNA sequence for clone 55154.

SEQ ID NO: 447 is the determined cDNA sequence for clone 55155.

SEQ ID NO: 448 is a first determined cDNA sequence for clone 55156.

SEQ ID NO: 449 is a second determined cDNA sequence for clone 55156.

SEQ ID NO: 450 is a first determined cDNA sequence for clone 55157.
SEQ ID NO: 451 is a second determined cDNA sequence for clone 55157.

SEQ ID NO: 452 is the determined cDNA sequence for clone 55158.
SEQ ID NO: 453 is the determined cDNA sequence for clone 55159.
SEQ ID NO: 454 is a first determined cDNA sequence for clone 55161.
SEQ ID NO: 455 is a second determined cDNA sequence for clone 55161.

SEQ ID NO: 456 is a first determined cDNA sequence for clone 55162.
SEQ ID NO: 457 is a second determined cDNA sequence for clone 55162.

SEQ ID NO: 458 is a first determined cDNA sequence for clone 55163.
SEQ ID NO: 459 is a second determined cDNA sequence for clone 55163.
SEQ ID NO: 460 is a first determined cDNA sequence for clone 55164.
SEQ ID NO: 461 is a second determined cDNA sequence for clone 55164.

SEQ ID NO: 462 is a first determined cDNA sequence for clone 55165.
SEQ ID NO: 463 is a second determined cDNA sequence for clone 55165.

SEQ ID NO: 464 is a first determined cDNA sequence for clone 55166.
SEQ ID NO: 465 is a second determined cDNA sequence for clone 55166.

SEQ ID NO: 466 is a first determined cDNA sequence for clone 55167.
SEQ ID NO: 467 is a second determined cDNA sequence for clone 55167.

SEQ ID NO: 468 is a first determined cDNA sequence for clone 55168.
SEQ ID NO: 469 is a second determined cDNA sequence for clone 55168.
SEQ ID NO: 470 is a first determined cDNA sequence for clone 55169.
SEQ ID NO: 471 is a second determined cDNA sequence for clone 55169.

SEQ ID NO: 472 is a first determined cDNA sequence for clone 55170.
SEQ ID NO: 473 is a second determined cDNA sequence for clone 55170.

SEQ ID NO: 474 is the determined cDNA sequence for clone 55171.

SEQ ID NO: 475 is the determined cDNA sequence for clone 55172.
SEQ ID NO: 476 is the determined cDNA sequence for clone 55173.
SEQ ID NO: 477 is a first determined cDNA sequence for clone 55174.
SEQ ID NO: 478 is a second determined cDNA sequence for clone 55174.
SEQ ID NO: 479 is the determined cDNA sequence for clone 55175.
SEQ ID NO: 480 is the determined cDNA sequence for clone 55176.
SEQ ID NO: 481 is the determined cDNA sequence for contig 525.
SEQ ID NO: 482 is the determined cDNA sequence for contig 526.
SEQ ID NO: 483 is the determined cDNA sequence for contig 527.
SEQ ID NO: 484 is the determined cDNA sequence for contig 528.
SEQ ID NO: 485 is the determined cDNA sequence for contig 529.
SEQ ID NO: 486 is the determined cDNA sequence for contig 530.
SEQ ID NO: 487 is the determined cDNA sequence for contig 531.
SEQ ID NO: 488 is the determined cDNA sequence for contig 532.
SEQ ID NO: 489 is the determined cDNA sequence for contig 533.
SEQ ID NO: 490 is the determined cDNA sequence for contig 534.
SEQ ID NO: 491 is the determined cDNA sequence for contig 535.
SEQ ID NO: 492 is the determined cDNA sequence for contig 536.
SEQ ID NO: 493 is the determined cDNA sequence for contig 537.
SEQ ID NO: 494 is the determined cDNA sequence for contig 538.
SEQ ID NO: 495 is the determined cDNA sequence for contig 539.
SEQ ID NO: 496 is the determined cDNA sequence for contig 540.
SEQ ID NO: 497 is the determined cDNA sequence for contig 541.
SEQ ID NO: 498 is the determined cDNA sequence for contig 542.
SEQ ID NO: 499 is the determined cDNA sequence for contig 543.
SEQ ID NO: 500 is the determined cDNA sequence for contig 544.
SEQ ID NO: 501 is the determined cDNA sequence for contig 545.
SEQ ID NO: 502 is the determined cDNA sequence for contig 546.
SEQ ID NO: 503 is the determined cDNA sequence for contig 547.
SEQ ID NO: 504 is the determined cDNA sequence for contig 548.
SEQ ID NO: 505 is the determined cDNA sequence for contig 549.
SEQ ID NO: 506 is the determined cDNA sequence for contig 550.
SEQ ID NO: 507 is the determined cDNA sequence for contig 551.
SEQ ID NO: 508 is the determined cDNA sequence for contig 552.
SEQ ID NO: 509 is the determined cDNA sequence for contig 553.

SEQ ID NO: 510 is the determined cDNA sequence for contig 554.
SEQ ID NO: 511 is the determined cDNA sequence for contig 555.
SEQ ID NO: 512 is the determined cDNA sequence for clone 57207.
SEQ ID NO: 513 is the determined cDNA sequence for clone 57209.
SEQ ID NO: 514 is the determined cDNA sequence for clone 57210.
SEQ ID NO: 515 is the determined cDNA sequence for clone 57211.
SEQ ID NO: 516 is the determined cDNA sequence for clone 57212.
SEQ ID NO: 517 is the determined cDNA sequence for clone 57213.
SEQ ID NO: 518 is the determined cDNA sequence for clone 57215.
SEQ ID NO: 519 is the determined cDNA sequence for clone 57219.
SEQ ID NO: 520 is the determined cDNA sequence for clone 57221.
SEQ ID NO: 521 is the determined cDNA sequence for clone 57222.
SEQ ID NO: 522 is the determined cDNA sequence for clone 57223.
SEQ ID NO: 523 is the determined cDNA sequence for clone 57225.
SEQ ID NO: 524 is the determined cDNA sequence for clone 57227.
SEQ ID NO: 525 is the determined cDNA sequence for clone 57228.
SEQ ID NO: 526 is the determined cDNA sequence for clone 57229.
SEQ ID NO: 527 is the determined cDNA sequence for clone 57230.
SEQ ID NO: 528 is the determined cDNA sequence for clone 57231.
SEQ ID NO: 529 is the determined cDNA sequence for clone 57232.
SEQ ID NO: 530 is the determined cDNA sequence for clone 57233.
SEQ ID NO: 531 is the determined cDNA sequence for clone 57234.
SEQ ID NO: 532 is the determined cDNA sequence for clone 57235.
SEQ ID NO: 533 is the determined cDNA sequence for clone 57236.
SEQ ID NO: 534 is the determined cDNA sequence for clone 57237.
SEQ ID NO: 535 is the determined cDNA sequence for clone 57238.
SEQ ID NO: 536 is the determined cDNA sequence for clone 57239.
SEQ ID NO: 537 is the determined cDNA sequence for clone 57240.
SEQ ID NO: 538 is the determined cDNA sequence for clone 57242.
SEQ ID NO: 539 is the determined cDNA sequence for clone 57243.
SEQ ID NO: 540 is the determined cDNA sequence for clone 57245.
SEQ ID NO: 541 is the determined cDNA sequence for clone 57248.
SEQ ID NO: 542 is the determined cDNA sequence for clone 57249.
SEQ ID NO: 543 is the determined cDNA sequence for clone 57250.
SEQ ID NO: 544 is the determined cDNA sequence for clone 57251.
SEQ ID NO: 545 is the determined cDNA sequence for clone 57253.

SEQ ID NO: 546 is the determined cDNA sequence for clone 57254.
SEQ ID NO: 547 is the determined cDNA sequence for clone 57255.
SEQ ID NO: 548 is the determined cDNA sequence for clone 57257.
SEQ ID NO: 549 is the determined cDNA sequence for clone 57258.
SEQ ID NO: 550 is the determined cDNA sequence for clone 57259.
SEQ ID NO: 551 is the determined cDNA sequence for clone 57261.
SEQ ID NO: 552 is the determined cDNA sequence for clone 57262.
SEQ ID NO: 553 is the determined cDNA sequence for clone 57263.
SEQ ID NO: 554 is the determined cDNA sequence for clone 57264.
SEQ ID NO: 555 is the determined cDNA sequence for clone 57265.
SEQ ID NO: 556 is the determined cDNA sequence for clone 57266.
SEQ ID NO: 557 is the determined cDNA sequence for clone 57267.
SEQ ID NO: 558 is the determined cDNA sequence for clone 57268.
SEQ ID NO: 559 is the determined cDNA sequence for clone 57269.
SEQ ID NO: 560 is the determined cDNA sequence for clone 57270.
SEQ ID NO: 561 is the determined cDNA sequence for clone 57271.
SEQ ID NO: 562 is the determined cDNA sequence for clone 57272.
SEQ ID NO: 563 is the determined cDNA sequence for clone 57274.
SEQ ID NO: 564 is the determined cDNA sequence for clone 57275.
SEQ ID NO: 565 is the determined cDNA sequence for clone 57277.
SEQ ID NO: 566 is the determined cDNA sequence for clone 57280.
SEQ ID NO: 567 is the determined cDNA sequence for clone 57281.
SEQ ID NO: 568 is the determined cDNA sequence for clone 57282.
SEQ ID NO: 569 is the determined cDNA sequence for clone 57283.
SEQ ID NO: 570 is the determined cDNA sequence for clone 57285.
SEQ ID NO: 571 is the determined cDNA sequence for clone 57287.
SEQ ID NO: 572 is the determined cDNA sequence for clone 57288.
SEQ ID NO: 573 is the determined cDNA sequence for clone 57289.
SEQ ID NO: 574 is the determined cDNA sequence for clone 57290.
SEQ ID NO: 575 is the determined cDNA sequence for clone 57292.
SEQ ID NO: 576 is the determined cDNA sequence for clone 57295.
SEQ ID NO: 577 is the determined cDNA sequence for clone 57296.
SEQ ID NO: 578 is the determined cDNA sequence for clone 57297.
SEQ ID NO: 579 is the determined cDNA sequence for clone 57299.
SEQ ID NO: 580 is the determined cDNA sequence for clone 57301.
SEQ ID NO: 581 is the determined cDNA sequence for clone 57302.

SEQ ID NO: 582 is the determined cDNA sequence for the beta chain of a lung tumor specific T cell receptor.

SEQ ID NO: 583 is the determined cDNA sequence for the alpha chain of a lung tumor specific T cell receptor.

SEQ ID NO: 584 is the amino acid sequence encoded by SEQ ID NO: 583.

SEQ ID NO: 585 is the amino acid sequence encoded by SEQ ID NO: 582.

SEQ ID NO: 586 is the amino acid sequence encoded by the 5' terminus of 14F10.

SEQ ID NO: 587 is the amino acid sequence of a T cell epitope contained within SEQ ID NO: 586.

SEQ ID NO:588 is the determined cDNA sequence for 54533

SEQ ID NO:589 is the determined cDNA sequence for 54534

SEQ ID NO:590 is the determined cDNA sequence for 54536

SEQ ID NO:591 is the determined cDNA sequence for 54538

SEQ ID NO:592 is the determined cDNA sequence for 54540

SEQ ID NO:593 is the determined cDNA sequence for 55084

SEQ ID NO:594 is the determined cDNA sequence for 55086

SEQ ID NO:595 is the determined cDNA sequence for 54555

SEQ ID NO:596 is the determined cDNA sequence for 54557

SEQ ID NO:597 is the determined cDNA sequence for 54564

SEQ ID NO:598 is the determined cDNA sequence for 55098

SEQ ID NO:599 is the determined cDNA sequence for 55473

SEQ ID NO:600 is the determined cDNA sequence for 55104

SEQ ID NO:601 is the determined cDNA sequence for 55105

SEQ ID NO:602 is the determined cDNA sequence for 55107

SEQ ID NO:603 is the determined cDNA sequence for 55108

SEQ ID NO:604 is the determined cDNA sequence for 55114

SEQ ID NO:605 is the determined cDNA sequence for 55477

SEQ ID NO:606 is the determined cDNA sequence for 55482

SEQ ID NO:607 is the determined cDNA sequence for 55483

SEQ ID NO:608 is the determined cDNA sequence for 55485

SEQ ID NO:609 is the determined cDNA sequence for 55487

SEQ ID NO:610 is the determined cDNA sequence for 55488

SEQ ID NO:611 is the determined cDNA sequence for 55087

SEQ ID NO:612 is the determined cDNA sequence for 55089
SEQ ID NO:613 is the determined cDNA sequence for 55092
SEQ ID NO:614 is the determined cDNA sequence for 55093
SEQ ID NO:615 is the determined cDNA sequence for 56926
SEQ ID NO:616 is the determined cDNA sequence for 56930
SEQ ID NO:617 is the determined cDNA sequence for 56944
SEQ ID NO:618 is the determined cDNA sequence for 56945
SEQ ID NO:619 is the determined cDNA sequence for 55490
SEQ ID NO:620 is the determined cDNA sequence for 55495
SEQ ID NO:621 is the determined cDNA sequence for 55504
SEQ ID NO:622 is the determined cDNA sequence for 55506
SEQ ID NO:623 is the determined cDNA sequence for 56480
SEQ ID NO:624 is the determined cDNA sequence for 56482
SEQ ID NO:625 is the determined cDNA sequence for 56484
SEQ ID NO:626 is the determined cDNA sequence for 56487
SEQ ID NO:627 is the determined cDNA sequence for 56488
SEQ ID NO:628 is the determined cDNA sequence for 56490
SEQ ID NO:629 is the determined cDNA sequence for 56493
SEQ ID NO:630 is the determined cDNA sequence for 56494
SEQ ID NO:631 is the determined cDNA sequence for 56495
SEQ ID NO:632 is the determined cDNA sequence for 56499
SEQ ID NO:633 is the determined cDNA sequence for 56517
SEQ ID NO:634 is the determined cDNA sequence for 56952
SEQ ID NO:635 is the determined cDNA sequence for 56953
SEQ ID NO:636 is the determined cDNA sequence for 56959
SEQ ID NO:637 is the determined cDNA sequence for 57139
SEQ ID NO:638 is the determined cDNA sequence for 57078
SEQ ID NO:639 is the determined cDNA sequence for 57092
SEQ ID NO:640 is the determined cDNA sequence for 57099
SEQ ID NO:641 is the determined cDNA sequence for 57100
SEQ ID NO:642 is the determined cDNA sequence for 57105
SEQ ID NO:643 is the determined cDNA sequence for 57111
SEQ ID NO:644 is the determined cDNA sequence for 57117
SEQ ID NO:645 is the determined cDNA sequence for 57121
SEQ ID NO:646 is the determined cDNA sequence for 57124
SEQ ID NO:647 is the determined cDNA sequence for 57125

SEQ ID NO:648-686 are the determined cDNA sequences for the clones described in Tables 9-10.

SEQ ID NO:687-727 are the determined cDNA sequences for the clones described in Tables 11-13.

SEQ ID NO:728 is the determined full-length cDNA sequence for clone DMS39 (partial sequence given in SEQ ID NO:695).

SEQ ID NO:729 is the determined full-length cDNA sequence for clone DMS126 (partial sequence given in SEQ ID NO:708).

SEQ ID NO:730 is the determined full-length cDNA sequence for clone DMS218 (partial sequence given in SEQ ID NO:720).

SEQ ID NO:731 is the determined full-length cDNA sequence for clone DMS253 (partial sequence given in SEQ ID NO:723).

SEQ ID NO:732 is the determined full-length cDNA sequence for clone LSCC-86 (partial sequence given in SEQ ID NO:665).

SEQ ID NO:733 is a first amino acid sequence encoded by SEQ ID NO:732 and designated LSCC-86protein1.

SEQ ID NO:734 is a second amino acid sequence encoded by SEQ ID NO:732 and designated LSCC-86protein2.

SEQ ID NO:735 is a third amino acid sequence encoded by SEQ ID NO:732 and designated LSCC-86protein3.

SEQ ID NO:736 is the determined full-length nucleic acid sequence of the cDNA insert contained in clone L86S-47.

SEQ ID NO:737 is the determined full-length nucleic acid sequence of the cDNA insert contained in clone L86S-39.

SEQ ID NO:738 is the predicted amino acid sequence corresponding to an open reading frame contained in SEQ ID NO:736.

SEQ ID NO:739 is the predicted amino acid sequence corresponding to an open reading frame contained in SEQ ID NO:737.

SEQ ID NO:740 is the determined nucleic acid sequence of a composite DNA clone containing an extended sequence related to SEQ ID NO:440.

SEQ ID NO:741 is the determined nucleic acid sequence of an open reading frame contained in SEQ ID NO: 740, identified by anchored PCR cloning, encoding the polypeptide designated L200T.

SEQ ID NO:742 is the predicted amino acid sequence of the polypeptide designated L200T encoded by the open reading frame set forth in SEQ ID NO:741.

SEQ ID NO:743 is the nucleic acid sequence of the cysteine/glutamate transporter corresponding to GenSeq No. Z16609.

SEQ ID NO:744 are the 47 additional nucleotides 5' of the first nucleotide of SEQ ID NO:440, identified by anchored PCR cloning.

SEQ ID NO:745 are the additional 16 amino acids encoded by the extended open reading frame of SEQ ID NO:741.

SEQ ID NO:746 is the nucleic acid sequence of human chromosome 4 corresponding to GenBank Accession number AC093903.

SEQ ID NO:747 is a nucleic acid sequence derived from SEQ ID NO:746 containing exon 1, intron 1 and exon 2 of L200T.

SEQ ID NO:748 is the oligonucleotide sequence of the forward PCR primer used to prepare a vector for recombinant L200T fusion protein expression in *E. coli* host cells.

SEQ ID NO:749 is the oligonucleotide sequence of the reverse PCR primer used to prepare a vector for recombinant L200T fusion protein expression in *E. coli* host cells.

DETAILED DESCRIPTION OF THE INVENTION

U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

The present invention is directed generally to compositions and their use in the therapy and diagnosis of cancer, particularly lung cancer. As described further below, illustrative compositions of the present invention include, but are not restricted to, polypeptides, particularly immunogenic polypeptides, polynucleotides encoding such polypeptides, antibodies and other binding agents, antigen presenting cells (APCs) and immune system cells (*e.g.,* T cells).

The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, et al. Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis et al. Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid

Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

All publications, patents and patent applications cited herein, whether supra or infra, are hereby incorporated by reference in their entirety.

As used in this specification and the appended claims, the singular forms "a," "an" and "the" include plural references unless the content clearly dictates otherwise.

Polypeptide Compositions

As used herein, the term "polypeptide" " is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising epitopes, *i.*e., antigenic determinants substantially responsible for the immunogenic properties of a polypeptide and being capable of evoking an immune response.

Particularly illustrative polypeptides of the present invention comprise those encoded by a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583 and 588-732, or a sequence that hybridizes under moderately stringent conditions, or, alternatively, under highly stringent conditions, to a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583 and 588-732. Certain other illustrative polypeptides of the invention comprise amino acid sequences as set forth in any one of SEQ ID NOs: 391, 393, 395, 397, 421, 425-427, 434-439, 584-587 and .

The polypeptides of the present invention are sometimes herein referred to as lung tumor proteins or lung tumor polypeptides, as an indication that their identification has been based at least in part upon their increased levels of expression in lung tumor samples. Thus, a "lung tumor polypeptide" or "lung tumor protein," refers generally to a polypeptide sequence of the present invention, or a polynucleotide

sequence encoding such a polypeptide, that is expressed in a substantial proportion of lung tumor samples, for example preferably greater than about 20%, more preferably greater than about 30%, and most preferably greater than about 50% or more of lung tumor samples tested, at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in normal tissues, as determined using a representative assay provided herein. A lung tumor polypeptide sequence of the invention, based upon its increased level of expression in tumor cells, has particular utility both as a diagnostic marker as well as a therapeutic target, as further described below.

In certain preferred embodiments, the polypeptides of the invention are immunogenic, *i.e.*, they react detectably within an immunoassay (such as an ELISA or T-cell stimulation assay) with antisera and/or T-cells from a patient with lung cancer. Screening for immunogenic activity can be performed using techniques well known to the skilled artisan. For example, such screens can be performed using methods such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In one illustrative example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, ^{125}I-labeled Protein A.

As would be recognized by the skilled artisan, immunogenic portions of the polypeptides disclosed herein are also encompassed by the present invention. An "immunogenic portion," as used herein, is a fragment of an immunogenic polypeptide of the invention that itself is immunologically reactive (*i.e.,* specifically binds) with the B-cells and/or T-cell surface antigen receptors that recognize the polypeptide. Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.,* they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well-known techniques.

In one preferred embodiment, an immunogenic portion of a polypeptide of the present invention is a portion that reacts with antisera and/or T-cells at a level that is not substantially less than the reactivity of the full-length polypeptide (*e.g.,* in an ELISA and/or T-cell reactivity assay). Preferably, the level of immunogenic activity of

the immunogenic portion is at least about 50%, preferably at least about 70% and most preferably greater than about 90% of the immunogenicity for the full-length polypeptide. In some instances, preferred immunogenic portions will be identified that have a level of immunogenic activity greater than that of the corresponding full-length polypeptide, *e.g.*, having greater than about 100% or 150% or more immunogenic activity.

In certain other embodiments, illustrative immunogenic portions may include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other illustrative immunogenic portions will contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

In another embodiment, a polypeptide composition of the invention may also comprise one or more polypeptides that are immunologically reactive with T cells and/or antibodies generated against a polypeptide of the invention, particularly a polypeptide having an amino acid sequence disclosed herein, or to an immunogenic fragment or variant thereof.

In another embodiment of the invention, polypeptides are provided that comprise one or more polypeptides that are capable of eliciting T cells and/or antibodies that are immunologically reactive with one or more polypeptides described herein, or one or more polypeptides encoded by contiguous nucleic acid sequences contained in the polynucleotide sequences disclosed herein, or immunogenic fragments or variants thereof, or to one or more nucleic acid sequences which hybridize to one or more of these sequences under conditions of moderate to high stringency.

The present invention, in another aspect, provides polypeptide fragments comprising at least about 5, 10, 15, 20, 25, 50, or 100 contiguous amino acids, or more, including all intermediate lengths, of a polypeptide compositions set forth herein, such as those set forth in SEQ ID NOs: 391, 393, 395, 397, 421, 425-427, 434-439, 584-587, 738, 739, 742, 745 and/or those encoded by a polynucleotide sequence set forth in a sequence of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746.

In another aspect, the present invention provides variants of the polypeptide compositions described herein. Polypeptide variants generally encompassed by the present invention will typically exhibit at least about 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described below), along its length, to a polypeptide sequences set forth herein.

In one preferred embodiment, the polypeptide fragments and variants provide by the present invention are immunologically reactive with an antibody and/or T-cell that reacts with a full-length polypeptide specifically set for the herein.

In another preferred embodiment, the polypeptide fragments and variants provided by the present invention exhibit a level of immunogenic activity of at least about 50%, preferably at least about 70%, and most preferably at least about 90% or more of that exhibited by a full-length polypeptide sequence specifically set forth herein.A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating their immunogenic activity as described herein and/or using any of a number of techniques well known in the art.

For example, certain illustrative variants of the polypeptides of the invention include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other illustrative variants include variants in which a small portion (*e.g.,* 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

In many instances, a variant will contain conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. As described above, modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, *e.g.*, with immunogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, immunogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence according to Table 1.

For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA

coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences which encode said peptides without appreciable loss of their biological utility or activity.

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TABLE 1

Amino Acids			Codons					
Alanine	Ala	A	GCA	GCC	GCG	GCU		
Cysteine	Cys	C	UGC	UGU				
Aspartic acid	Asp	D	GAC	GAU				
Glutamic acid	Glu	E	GAA	GAG				
Phenylalanine	Phe	F	UUC	UUU				
Glycine	Gly	G	GGA	GGC	GGG	GGU		
Histidine	His	H	CAC	CAU				
Isoleucine	Ile	I	AUA	AUC	AUU			
Lysine	Lys	K	AAA	AAG				
Leucine	Leu	L	UUA	UUG	CUA	CUC	CUG	CUU
Methionine	Met	M	AUG					
Asparagine	Asn	N	AAC	AAU				
Proline	Pro	P	CCA	CCC	CCG	CCU		
Glutamine	Gln	Q	CAA	CAG				
Arginine	Arg	R	AGA	AGG	CGA	CGC	CGG	CGU
Serine	Ser	S	AGC	AGU	UCA	UCC	UCG	UCU
Threonine	Thr	T	ACA	ACC	ACG	ACU		
Valine	Val	V	GUA	GUC	GUG	GUU		
Tryptophan	Trp	W	UGG					
Tyrosine	Tyr	Y	UAC	UAU				

In making such changes, the hydropathic index of amino acids may be considered. The importance of the hydropathic amino acid index in conferring 10 interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982, incorporated herein by reference). It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of the

resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (–0.4); threonine (–0.7); serine (–0.8); tryptophan (–0.9); tyrosine (–1.3); proline (–1.6); histidine (–3.2); glutamate (–3.5); glutamine (–3.5); aspartate (–3.5); asparagine (–3.5); lysine (–3.9); and arginine (–4.5).

It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydropathic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydropathic indices are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 (specifically incorporated herein by reference in its entirety), states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 ± 1); glutamate (+3.0 ± 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (–0.4); proline (–0.5 ± 1); alanine (–0.5); histidine (–0.5); cysteine (–1.0); methionine (–1.3); valine (–1.5); leucine (–1.8); isoleucine (–1.8); tyrosine (–2.3); phenylalanine (–2.5); tryptophan (–3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ±2 is preferred, those within ±1 are particularly preferred, and those within ±0.5 are even more particularly preferred.

As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

In addition, any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.,* poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

When comparing polypeptide sequences, two sequences are said to be "identical" if the sequence of amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a

reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is

reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

In one preferred approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Within other illustrative embodiments, a polypeptide may be a fusion polypeptide that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the polypeptide or to enable the polypeptide to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the polypeptide.

Fusion polypeptides may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion polypeptide is expressed as a recombinant polypeptide, allowing the production of increased levels, relative to a non-fused polypeptide, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion polypeptide that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and second polypeptide components by a distance sufficient to ensure that each polypeptide

folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion polypeptide using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., *Gene 40*:39-46, 1985; Murphy et al., *Proc. Natl. Acad. Sci. USA 83*:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

The fusion polypeptide can comprise a polypeptide as described herein together with an unrelated immunogenic protein, such as an immunogenic protein capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (*see*, for example, Stoute et al. *New Engl. J. Med.*, *336*:86-91, 1997).

In one preferred embodiment, the immunological fusion partner is derived from a Mycobacterium sp., such as a Mycobacterium tuberculosis-derived Ra12 fragment. Ra12 compositions and methods for their use in enhancing the expression and/or immunogenicity of heterologous polynucleotide/polypeptide sequences is described in U.S. Patent Application 60/158,585, the disclosure of which is incorporated herein by reference in its entirety. Briefly, Ra12 refers to a polynucleotide region that is a subsequence of a *Mycobacterium tuberculosis* MTB32A nucleic acid. MTB32A is a serine protease of 32 KD molecular weight encoded by a gene in virulent and avirulent strains of *M. tuberculosis*. The nucleotide sequence and amino acid sequence of MTB32A have been described (for example, U.S. Patent Application

60/158,585; see also, Skeiky *et al.*, *Infection and Immun.* (1999) 67:3998-4007, incorporated herein by reference). C-terminal fragments of the MTB32A coding sequence express at high levels and remain as a soluble polypeptides throughout the purification process. Moreover, Ral2 may enhance the immunogenicity of heterologous immunogenic polypeptides with which it is fused. One preferred Ral2 fusion polypeptide comprises a 14 KD C-terminal fragment corresponding to amino acid residues 192 to 323 of MTB32A. Other preferred Ral2 polynucleotides generally comprise at least about 15 consecutive nucleotides, at least about 30 nucleotides, at least about 60 nucleotides, at least about 100 nucleotides, at least about 200 nucleotides, or at least about 300 nucleotides that encode a portion of a Ral2 polypeptide. Ral2 polynucleotides may comprise a native sequence (*i.e.,* an endogenous sequence that encodes a Ral2 polypeptide or a portion thereof) or may comprise a variant of such a sequence. Ral2 polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the biological activity of the encoded fusion polypeptide is not substantially diminished, relative to a fusion polypeptide comprising a native Ral2 polypeptide. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native Ral2 polypeptide or a portion thereof.

Within other preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (*e.g.,* the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in *E. coli* (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan

backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10*:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion polypeptide. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

Yet another illustrative embodiment involves fusion polypeptides, and the polynucleotides encoding them, wherein the fusion partner comprises a targeting signal capable of directing a polypeptide to the endosomal/lysosomal compartment, as described in U.S. Patent No. 5,633,234. An immunogenic polypeptide of the invention, when fused with this targeting signal, will associate more efficiently with MHC class II molecules and thereby provide enhanced in vivo stimulation of $CD4^+$ T-cells specific for the polypeptide.

Polypeptides of the invention are prepared using any of a variety of well known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc. 85*:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

In general, polypeptide compositions (including fusion polypeptides) of the invention are isolated. An "isolated" polypeptide is one that is removed from its original environment. For example, a naturally-occurring protein or polypeptide is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are also purified, *e.g.*, are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure.

Polynucleotide Compositions

The present invention, in other aspects, provides polynucleotide compositions. The terms "DNA" and "polynucleotide" are used essentially interchangeably herein to refer to a DNA molecule that has been isolated free of total genomic DNA of a particular species. "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

As will be understood by those skilled in the art, the polynucleotide compositions of this invention can include genomic sequences, extra-genomic and plasmid-encoded sequences and smaller engineered gene segments that express, or may be adapted to express, proteins, polypeptides, peptides and the like. Such segments may be naturally isolated, or modified synthetically by the hand of man.

As will be also recognized by the skilled artisan, polynucleotides of the invention may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules may include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (*i.e.,* an endogenous sequence that encodes a polypeptide/protein of the invention or a portion thereof) or may comprise a sequence that encodes a variant or derivative, preferably and immunogenic variant or derivative, of such a sequence.

Therefore, according to another aspect of the present invention, polynucleotide compositions are provided that comprise some or all of a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746, complements of a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746, and degenerate variants of a polynucleotide sequence set forth in any one of SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740,

741, 744 and 746. In certain preferred embodiments, the polynucleotide sequences set forth herein encode immunogenic polypeptides, as described above.

In other related embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein in SEQ ID NOs: 217-390, 392, 394, 396, 398-420 422-424, 428-433, 440-583, 588-732, 736, 737, 740, 741, 744 and 746, for example those comprising at least 70% sequence identity, preferably at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher, sequence identity compared to a polynucleotide sequence of this invention using the methods described herein, (*e.g.*, BLAST analysis using standard parameters, as described below). One skilled in this art will recognize that these values can be appropriately adjusted to determine corresponding identity of proteins encoded by two nucleotide sequences by taking into account codon degeneracy, amino acid similarity, reading frame positioning and the like.

Typically, polynucleotide variants will contain one or more substitutions, additions, deletions and/or insertions, preferably such that the immunogenicity of the polypeptide encoded by the variant polynucleotide is not substantially diminished relative to a polypeptide encoded by a polynucleotide sequence specifically set forth herein). The term "variants" should also be understood to encompasses homologous genes of xenogenic origin.

In additional embodiments, the present invention provides polynucleotide fragments comprising various lengths of contiguous stretches of sequence identical to or complementary to one or more of the sequences disclosed herein. For example, polynucleotides are provided by this invention that comprise at least about 10, 15, 20, 30, 40, 50, 75, 100, 150, 200, 300, 400, 500 or 1000 or more contiguous nucleotides of one or more of the sequences disclosed herein as well as all intermediate lengths there between. It will be readily understood that "intermediate lengths", in this context, means any length between the quoted values, such as 16, 17, 18, 19, *etc.*; 21, 22, 23, *etc.*; 30, 31, 32, *etc.*; 50, 51, 52, 53, *etc.*; 100, 101, 102, 103, *etc.*; 150, 151, 152, 153, *etc.*; including all integers through 200-500; 500-1,000, and the like.

In another embodiment of the invention, polynucleotide compositions are provided that are capable of hybridizing under moderate to high stringency conditions to a polynucleotide sequence provided herein, or a fragment thereof, or a complementary sequence thereof. Hybridization techniques are well known in the art of molecular biology. For purposes of illustration, suitable moderately stringent conditions for testing the hybridization of a polynucleotide of this invention with other polynucleotides

include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-60°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS. One skilled in the art will understand that the stringency of hybridization can be readily manipulated, such as by altering the salt content of the hybridization solution and/or the temperature at which the hybridization is performed. For example, in another embodiment, suitable highly stringent hybridization conditions include those described above, with the exception that the temperature of hybridization is increased, *e.g.*, to 60-65°C or 65-70°C.

In certain preferred embodiments, the polynucleotides described above, *e.g.*, polynucleotide variants, fragments and hybridizing sequences, encode polypeptides that are immunologically cross-reactive with a polypeptide sequence specifically set forth herein. In other preferred embodiments, such polynucleotides encode polypeptides that have a level of immunogenic activity of at least about 50%, preferably at least about 70%, and more preferably at least about 90% of that for a polypeptide sequence specifically set forth herein.

The polynucleotides of the present invention, or fragments thereof, regardless of the length of the coding sequence itself, may be combined with other DNA sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant DNA protocol. For example, illustrative polynucleotide segments with total lengths of about 10,000, about 5000, about 3000, about 2,000, about 1,000, about 500, about 200, about 100, about 50 base pairs in length, and the like, (including all intermediate lengths) are contemplated to be useful in many implementations of this invention.

When comparing polynucleotide sequences, two sequences are said to be "identical" if the sequence of nucleotides in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the polynucleotides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X

determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Therefore, in another embodiment of the invention, a mutagenesis approach, such as site-specific mutagenesis, is employed for the preparation of immunogenic variants and/or derivatives of the polypeptides described herein. By this approach, specific modifications in a polypeptide sequence can be made through mutagenesis of the underlying polynucleotides that encode them. These techniques provides a straightforward approach to prepare and test sequence variants, for example, incorporating one or more of the foregoing considerations, by introducing one or more nucleotide sequence changes into the polynucleotide.

Site-specific mutagenesis allows the production of mutants through the use of specific oligonucleotide sequences which encode the DNA sequence of the desired mutation, as well as a sufficient number of adjacent nucleotides, to provide a primer sequence of sufficient size and sequence complexity to form a stable duplex on both sides of the deletion junction being traversed. Mutations may be employed in a selected polynucleotide sequence to improve, alter, decrease, modify, or otherwise change the properties of the polynucleotide itself, and/or alter the properties, activity, composition, stability, or primary sequence of the encoded polypeptide.

In certain embodiments of the present invention, the inventors contemplate the mutagenesis of the disclosed polynucleotide sequences to alter one or more properties of the encoded polypeptide, such as the immunogenicity of a polypeptide vaccine. The techniques of site-specific mutagenesis are well known in the art, and are widely used to create variants of both polypeptides and polynucleotides. For example, site-specific mutagenesis is often used to alter a specific portion of a DNA molecule. In such embodiments, a primer comprising typically about 14 to about 25 nucleotides or so in length is employed, with about 5 to about 10 residues on both sides of the junction of the sequence being altered.

As will be appreciated by those of skill in the art, site-specific mutagenesis techniques have often employed a phage vector that exists in both a single stranded and double stranded form. Typical vectors useful in site-directed mutagenesis include vectors such as the M13 phage. These phage are readily commercially-available and their use is generally well-known to those skilled in the art. Double-stranded plasmids are also routinely employed in site directed mutagenesis that eliminates the step of transferring the gene of interest from a plasmid to a phage.

In general, site-directed mutagenesis in accordance herewith is performed by first obtaining a single-stranded vector or melting apart of two strands of a double-stranded vector that includes within its sequence a DNA sequence that encodes the desired peptide. An oligonucleotide primer bearing the desired mutated sequence is prepared, generally synthetically. This primer is then annealed with the single-stranded vector, and subjected to DNA polymerizing enzymes such as *E. coli* polymerase I Klenow fragment, in order to complete the synthesis of the mutation-bearing strand. Thus, a heteroduplex is formed wherein one strand encodes the original non-mutated sequence and the second strand bears the desired mutation. This heteroduplex vector is then used to transform appropriate cells, such as *E. coli* cells, and clones are selected which include recombinant vectors bearing the mutated sequence arrangement.

The preparation of sequence variants of the selected peptide-encoding DNA segments using site-directed mutagenesis provides a means of producing potentially useful species and is not meant to be limiting as there are other ways in which sequence variants of peptides and the DNA sequences encoding them may be obtained. For example, recombinant vectors encoding the desired peptide sequence may be treated with mutagenic agents, such as hydroxylamine, to obtain sequence variants. Specific details regarding these methods and protocols are found in the teachings of Maloy *et al.*, 1994; Segal, 1976; Prokop and Bajpai, 1991; Kuby, 1994; and Maniatis *et al.*, 1982, each incorporated herein by reference, for that purpose.

As used herein, the term "oligonucleotide directed mutagenesis procedure" refers to template-dependent processes and vector-mediated propagation which result in an increase in the concentration of a specific nucleic acid molecule relative to its initial concentration, or in an increase in the concentration of a detectable signal, such as amplification. As used herein, the term "oligonucleotide directed mutagenesis procedure" is intended to refer to a process that involves the template-dependent extension of a primer molecule. The term template dependent process refers to nucleic acid synthesis of an RNA or a DNA molecule wherein the sequence of the newly synthesized strand of nucleic acid is dictated by the well-known rules of complementary base pairing (see, for example, Watson, 1987). Typically, vector mediated methodologies involve the introduction of the nucleic acid fragment into a DNA or RNA vector, the clonal amplification of the vector, and the recovery of the amplified nucleic acid fragment. Examples of such methodologies are provided by U. S. Patent No. 4,237,224, specifically incorporated herein by reference in its entirety.

In another approach for the production of polypeptide variants of the present invention, recursive sequence recombination, as described in U.S. Patent No. 5,837,458, may be employed. In this approach, iterative cycles of recombination and screening or selection are performed to "evolve" individual polynucleotide variants of the invention having, for example, enhanced immunogenic activity.

In other embodiments of the present invention, the polynucleotide sequences provided herein can be advantageously used as probes or primers for nucleic acid hybridization. As such, it is contemplated that nucleic acid segments that comprise a sequence region of at least about 15 nucleotide long contiguous sequence that has the same sequence as, or is complementary to, a 15 nucleotide long contiguous sequence disclosed herein will find particular utility. Longer contiguous identical or complementary sequences, *e.g.*, those of about 20, 30, 40, 50, 100, 200, 500, 1000

(including all intermediate lengths) and even up to full length sequences will also be of use in certain embodiments.

The ability of such nucleic acid probes to specifically hybridize to a sequence of interest will enable them to be of use in detecting the presence of complementary sequences in a given sample. However, other uses are also envisioned, such as the use of the sequence information for the preparation of mutant species primers, or primers for use in preparing other genetic constructions.

Polynucleotide molecules having sequence regions consisting of contiguous nucleotide stretches of 10-14, 15-20, 30, 50, or even of 100-200 nucleotides or so (including intermediate lengths as well), identical or complementary to a polynucleotide sequence disclosed herein, are particularly contemplated as hybridization probes for use in, *e.g.*, Southern and Northern blotting. This would allow a gene product, or fragment thereof, to be analyzed, both in diverse cell types and also in various bacterial cells. The total size of fragment, as well as the size of the complementary stretch(es), will ultimately depend on the intended use or application of the particular nucleic acid segment. Smaller fragments will generally find use in hybridization embodiments, wherein the length of the contiguous complementary region may be varied, such as between about 15 and about 100 nucleotides, but larger contiguous complementarity stretches may be used, according to the length complementary sequences one wishes to detect.

The use of a hybridization probe of about 15-25 nucleotides in length allows the formation of a duplex molecule that is both stable and selective. Molecules having contiguous complementary sequences over stretches greater than 15 bases in length are generally preferred, though, in order to increase stability and selectivity of the hybrid, and thereby improve the quality and degree of specific hybrid molecules obtained. One will generally prefer to design nucleic acid molecules having gene-complementary stretches of 15 to 25 contiguous nucleotides, or even longer where desired.

Hybridization probes may be selected from any portion of any of the sequences disclosed herein. All that is required is to review the sequences set forth herein, or to any continuous portion of the sequences, from about 15-25 nucleotides in length up to and including the full length sequence, that one wishes to utilize as a probe or primer. The choice of probe and primer sequences may be governed by various factors. For example, one may wish to employ primers from towards the termini of the total sequence.

Small polynucleotide segments or fragments may be readily prepared by, for example, directly synthesizing the fragment by chemical means, as is commonly practiced using an automated oligonucleotide synthesizer. Also, fragments may be obtained by application of nucleic acid reproduction technology, such as the PCR™ technology of U. S. Patent 4,683,202 (incorporated herein by reference), by introducing selected sequences into recombinant vectors for recombinant production, and by other recombinant DNA techniques generally known to those of skill in the art of molecular biology.

The nucleotide sequences of the invention may be used for their ability to selectively form duplex molecules with complementary stretches of the entire gene or gene fragments of interest. Depending on the application envisioned, one will typically desire to employ varying conditions of hybridization to achieve varying degrees of selectivity of probe towards target sequence. For applications requiring high selectivity, one will typically desire to employ relatively stringent conditions to form the hybrids, *e.g.*, one will select relatively low salt and/or high temperature conditions, such as provided by a salt concentration of from about 0.02 M to about 0.15 M salt at temperatures of from about 50°C to about 70°C. Such selective conditions tolerate little, if any, mismatch between the probe and the template or target strand, and would be particularly suitable for isolating related sequences.

Of course, for some applications, for example, where one desires to prepare mutants employing a mutant primer strand hybridized to an underlying template, less stringent (reduced stringency) hybridization conditions will typically be needed in order to allow formation of the heteroduplex. In these circumstances, one may desire to employ salt conditions such as those of from about 0.15 M to about 0.9 M salt, at temperatures ranging from about 20°C to about 55°C. Cross-hybridizing species can thereby be readily identified as positively hybridizing signals with respect to control hybridizations. In any case, it is generally appreciated that conditions can be rendered more stringent by the addition of increasing amounts of formamide, which serves to destabilize the hybrid duplex in the same manner as increased temperature. Thus, hybridization conditions can be readily manipulated, and thus will generally be a method of choice depending on the desired results.

According to another embodiment of the present invention, polynucleotide compositions comprising antisense oligonucleotides are provided. Antisense oligonucleotides have been demonstrated to be effective and targeted inhibitors of protein synthesis, and, consequently, provide a therapeutic approach by which a disease can be treated by inhibiting the synthesis of proteins that contribute to

the disease. The efficacy of antisense oligonucleotides for inhibiting protein synthesis is well established. For example, the synthesis of polygalactauronase and the muscarine type 2 acetylcholine receptor are inhibited by antisense oligonucleotides directed to their respective mRNA sequences (U. S. Patent 5,739,119 and U. S. Patent 5,759,829). Further, examples of antisense inhibition have been demonstrated with the nuclear protein cyclin, the multiple drug resistance gene (MDG1), ICAM-1, E-selectin, STK-1, striatal $GABA_A$ receptor and human EGF (Jaskulski *et al.*, Science. 1988 Jun 10;240(4858):1544-6; Vasanthakumar and Ahmed, Cancer Commun. 1989;1(4):225-32; Peris *et al.*, Brain Res Mol Brain Res. 1998 Jun 15;57(2):310-20; U. S. Patent 5,801,154; U.S. Patent 5,789,573; U. S. Patent 5,718,709 and U.S. Patent 5,610,288). Antisense constructs have also been described that inhibit and can be used to treat a variety of abnormal cellular proliferations, *e.g.* cancer (U. S. Patent 5,747,470; U. S. Patent 5,591,317 and U. S. Patent 5,783,683).

Therefore, in certain embodiments, the present invention provides oligonucleotide sequences that comprise all, or a portion of, any sequence that is capable of specifically binding to polynucleotide sequence described herein, or a complement thereof. In one embodiment, the antisense oligonucleotides comprise DNA or derivatives thereof. In another embodiment, the oligonucleotides comprise RNA or derivatives thereof. In a third embodiment, the oligonucleotides are modified DNAs comprising a phosphorothioated modified backbone. In a fourth embodiment, the oligonucleotide sequences comprise peptide nucleic acids or derivatives thereof. In each case, preferred compositions comprise a sequence region that is complementary, and more preferably substantially-complementary, and even more preferably, completely complementary to one or more portions of polynucleotides disclosed herein. Selection of antisense compositions specific for a given gene sequence is based upon analysis of the chosen target sequence and determination of secondary structure, T_m, binding energy, and relative stability. Antisense compositions may be selected based upon their relative inability to form dimers, hairpins, or other secondary structures that would reduce or prohibit specific binding to the target mRNA in a host cell. Highly preferred target regions of the mRNA, are those which are at or near the AUG translation initiation codon, and those sequences which are substantially complementary to 5' regions of the mRNA. These secondary structure analyses and target site selection considerations can be performed, for example, using v.4 of the OLIGO primer analysis software and/or the BLASTN 2.0.5 algorithm software (Altschul *et al.*, Nucleic Acids Res. 1997, 25(17):3389-402).

The use of an antisense delivery method employing a short peptide vector, termed MPG (27 residues), is also contemplated. The MPG peptide contains a hydrophobic domain derived from the fusion sequence of HIV gp41 and a hydrophilic domain from the nuclear localization sequence of SV40 T-antigen (Morris *et al.*, Nucleic Acids Res. 1997 Jul 15;25(14):2730-6). It has been demonstrated that several molecules of the MPG peptide coat the antisense oligonucleotides and can be delivered into cultured mammalian cells in less than 1 hour with relatively high efficiency (90%). Further, the interaction with MPG strongly increases both the stability of the oligonucleotide to nuclease and the ability to cross the plasma membrane.

According to another embodiment of the invention, the polynucleotide compositions described herein are used in the design and preparation of ribozyme molecules for inhibiting expression of the tumor polypeptides and proteins of the present invention in tumor cells. Ribozymes are RNA-protein complexes that cleave nucleic acids in a site-specific fashion. Ribozymes have specific catalytic domains that possess endonuclease activity (Kim and Cech, Proc Natl Acad Sci U S A. 1987 Dec;84(24):8788-92; Forster and Symons, Cell. 1987 Apr 24;49(2):211-20). For example, a large number of ribozymes accelerate phosphoester transfer reactions with a high degree of specificity, often cleaving only one of several phosphoesters in an oligonucleotide substrate (Cech *et al.*, Cell. 1981 Dec;27(3 Pt 2):487-96; Michel and Westhof, J Mol Biol. 1990 Dec 5;216(3):585-610; Reinhold-Hurek and Shub, Nature. 1992 May 14;357(6374):173-6). This specificity has been attributed to the requirement that the substrate bind via specific base-pairing interactions to the internal guide sequence ("IGS") of the ribozyme prior to chemical reaction.

Six basic varieties of naturally occurring enzymatic RNAs are known presently. Each can catalyze the hydrolysis of RNA phosphodiester bonds *in trans* (and thus can cleave other RNA molecules) under physiological conditions. In general, enzymatic nucleic acids act by first binding to a target RNA. Such binding occurs through the target binding portion of a enzymatic nucleic acid which is held in close proximity to an enzymatic portion of the molecule that acts to cleave the target RNA. Thus, the enzymatic nucleic acid first recognizes and then binds a target RNA through complementary base-pairing, and once bound to the correct site, acts enzymatically to cut the target RNA. Strategic cleavage of such a target RNA will destroy its ability to direct synthesis of an encoded protein. After an enzymatic nucleic acid has bound and cleaved its RNA target, it is released from that RNA to search for another target and can repeatedly bind and cleave new targets.

The enzymatic nature of a ribozyme is advantageous over many technologies, such as antisense technology (where a nucleic acid molecule simply binds to a nucleic acid target to block its translation) since the concentration of ribozyme necessary to affect a therapeutic treatment is lower than that of an antisense oligonucleotide. This advantage reflects the ability of the ribozyme to act enzymatically. Thus, a single ribozyme molecule is able to cleave many molecules of target RNA. In addition, the ribozyme is a highly specific inhibitor, with the specificity of inhibition depending not only on the base pairing mechanism of binding to the target RNA, but also on the mechanism of target RNA cleavage. Single mismatches, or base-substitutions, near the site of cleavage can completely eliminate catalytic activity of a ribozyme. Similar mismatches in antisense molecules do not prevent their action (Woolf *et al.*, Proc Natl Acad Sci U S A. 1992 Aug 15;89(16):7305-9). Thus, the specificity of action of a ribozyme is greater than that of an antisense oligonucleotide binding the same RNA site.

The enzymatic nucleic acid molecule may be formed in a hammerhead, hairpin, a hepatitis δ virus, group I intron or RNaseP RNA (in association with an RNA guide sequence) or Neurospora VS RNA motif. Examples of hammerhead motifs are described by Rossi *et al.* Nucleic Acids Res. 1992 Sep 11;20(17):4559-65. Examples of hairpin motifs are described by Hampel *et al.* (Eur. Pat. Appl. Publ. No. EP 0360257), Hampel and Tritz, Biochemistry 1989 Jun 13;28(12):4929-33; Hampel *et al.*, Nucleic Acids Res. 1990 Jan 25;18(2):299-304 and U. S. Patent 5,631,359. An example of the hepatitis δ virus motif is described by Perrotta and Been, Biochemistry. 1992 Dec 1;31(47):11843-52; an example of the RNaseP motif is described by Guerrier-Takada *et al.*, Cell. 1983 Dec;35(3 Pt 2):849-57; Neurospora VS RNA ribozyme motif is described by Collins (Saville and Collins, Cell. 1990 May 18;61(4):685-96; Saville and Collins, Proc Natl Acad Sci U S A. 1991 Oct 1;88(19):8826-30; Collins and Olive, Biochemistry. 1993 Mar 23;32(11):2795-9); and an example of the Group I intron is described in (U. S. Patent 4,987,071). All that is important in an enzymatic nucleic acid molecule of this invention is that it has a specific substrate binding site which is complementary to one or more of the target gene RNA regions, and that it have nucleotide sequences within or surrounding that substrate binding site which impart an RNA cleaving activity to the molecule. Thus the ribozyme constructs need not be limited to specific motifs mentioned herein.

Ribozymes may be designed as described in Int. Pat. Appl. Publ. No. WO 93/23569 and Int. Pat. Appl. Publ. No. WO 94/02595, each specifically incorporated herein by reference) and synthesized to be tested *in vitro* and *in vivo*, as

described. Such ribozymes can also be optimized for delivery. While specific examples are provided, those in the art will recognize that equivalent RNA targets in other species can be utilized when necessary.

Ribozyme activity can be optimized by altering the length of the ribozyme binding arms, or chemically synthesizing ribozymes with modifications that prevent their degradation by serum ribonucleases (see *e.g.*, Int. Pat. Appl. Publ. No. WO 92/07065; Int. Pat. Appl. Publ. No. WO 93/15187; Int. Pat. Appl. Publ. No. WO 91/03162; Eur. Pat. Appl. Publ. No. 92110298.4; U. S. Patent 5,334,711; and Int. Pat. Appl. Publ. No. WO 94/13688, which describe various chemical modifications that can be made to the sugar moieties of enzymatic RNA molecules), modifications which enhance their efficacy in cells, and removal of stem II bases to shorten RNA synthesis times and reduce chemical requirements.

Sullivan *et al.* (Int. Pat. Appl. Publ. No. WO 94/02595) describes the general methods for delivery of enzymatic RNA molecules. Ribozymes may be administered to cells by a variety of methods known to those familiar to the art, including, but not restricted to, encapsulation in liposomes, by iontophoresis, or by incorporation into other vehicles, such as hydrogels, cyclodextrins, biodegradable nanocapsules, and bioadhesive microspheres. For some indications, ribozymes may be directly delivered *ex vivo* to cells or tissues with or without the aforementioned vehicles. Alternatively, the RNA/vehicle combination may be locally delivered by direct inhalation, by direct injection or by use of a catheter, infusion pump or stent. Other routes of delivery include, but are not limited to, intravascular, intramuscular, subcutaneous or joint injection, aerosol inhalation, oral (tablet or pill form), topical, systemic, ocular, intraperitoneal and/or intrathecal delivery. More detailed descriptions of ribozyme delivery and administration are provided in Int. Pat. Appl. Publ. No. WO 94/02595 and Int. Pat. Appl. Publ. No. WO 93/23569, each specifically incorporated herein by reference.

Another means of accumulating high concentrations of a ribozyme(s) within cells is to incorporate the ribozyme-encoding sequences into a DNA expression vector. Transcription of the ribozyme sequences are driven from a promoter for eukaryotic RNA polymerase I (pol I), RNA polymerase II (pol II), or RNA polymerase III (pol III). Transcripts from pol II or pol III promoters will be expressed at high levels in all cells; the levels of a given pol II promoter in a given cell type will depend on the nature of the gene regulatory sequences (enhancers, silencers, *etc.*) present nearby. Prokaryotic RNA polymerase promoters may also be used, providing that the prokaryotic RNA polymerase enzyme is expressed in the appropriate cells. Ribozymes

expressed from such promoters have been shown to function in mammalian cells. Such transcription units can be incorporated into a variety of vectors for introduction into mammalian cells, including but not restricted to, plasmid DNA vectors, viral DNA vectors (such as adenovirus or adeno-associated vectors), or viral RNA vectors (such as retroviral, semliki forest virus, sindbis virus vectors).

In another embodiment of the invention, peptide nucleic acids (PNAs) compositions are provided. PNA is a DNA mimic in which the nucleobases are attached to a pseudopeptide backbone (Good and Nielsen, Antisense Nucleic Acid Drug Dev. 1997 7(4) 431-37). PNA is able to be utilized in a number methods that traditionally have used RNA or DNA. Often PNA sequences perform better in techniques than the corresponding RNA or DNA sequences and have utilities that are not inherent to RNA or DNA. A review of PNA including methods of making, characteristics of, and methods of using, is provided by Corey (*Trends Biotechnol* 1997 Jun;15(6):224-9). As such, in certain embodiments, one may prepare PNA sequences that are complementary to one or more portions of the ACE mRNA sequence, and such PNA compositions may be used to regulate, alter, decrease, or reduce the translation of ACE-specific mRNA, and thereby alter the level of ACE activity in a host cell to which such PNA compositions have been administered.

PNAs have 2-aminoethyl-glycine linkages replacing the normal phosphodiester backbone of DNA (Nielsen *et al.*, *Science* 1991 Dec 6;254(5037):1497-500; Hanvey *et al.*, Science. 1992 Nov 27;258(5087):1481-5; Hyrup and Nielsen, Bioorg Med Chem. 1996 Jan;4(1):5-23). This chemistry has three important consequences: firstly, in contrast to DNA or phosphorothioate oligonucleotides, PNAs are neutral molecules; secondly, PNAs are achiral, which avoids the need to develop a stereoselective synthesis; and thirdly, PNA synthesis uses standard Boc or Fmoc protocols for solid-phase peptide synthesis, although other methods, including a modified Merrifield method, have been used.

PNA monomers or ready-made oligomers are commercially available from PerSeptive Biosystems (Framingham, MA). PNA syntheses by either Boc or Fmoc protocols are straightforward using manual or automated protocols (Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45). The manual protocol lends itself to the production of chemically modified PNAs or the simultaneous synthesis of families of closely related PNAs.

As with peptide synthesis, the success of a particular PNA synthesis will depend on the properties of the chosen sequence. For example, while in theory PNAs can incorporate any combination of nucleotide bases, the presence of adjacent purines

can lead to deletions of one or more residues in the product. In expectation of this difficulty, it is suggested that, in producing PNAs with adjacent purines, one should repeat the coupling of residues likely to be added inefficiently. This should be followed by the purification of PNAs by reverse-phase high-pressure liquid chromatography, providing yields and purity of product similar to those observed during the synthesis of peptides.

Modifications of PNAs for a given application may be accomplished by coupling amino acids during solid-phase synthesis or by attaching compounds that contain a carboxylic acid group to the exposed N-terminal amine. Alternatively, PNAs can be modified after synthesis by coupling to an introduced lysine or cysteine. The ease with which PNAs can be modified facilitates optimization for better solubility or for specific functional requirements. Once synthesized, the identity of PNAs and their derivatives can be confirmed by mass spectrometry. Several studies have made and utilized modifications of PNAs (for example, Norton *et al.*, Bioorg Med Chem. 1995 Apr;3(4):437-45; Petersen *et al.*, J Pept Sci. 1995 May-Jun;1(3):175-83; Orum *et al.*, Biotechniques. 1995 Sep;19(3):472-80; Footer *et al.*, Biochemistry. 1996 Aug 20;35(33):10673-9; Griffith *et al.*, Nucleic Acids Res. 1995 Aug 11;23(15):3003-8; Pardridge *et al.*, Proc Natl Acad Sci U S A. 1995 Jun 6;92(12):5592-6; Boffa *et al.*, Proc Natl Acad Sci U S A. 1995 Mar 14;92(6):1901-5; Gambacorti-Passerini *et al.*, Blood. 1996 Aug 15;88(4):1411-7; Armitage *et al.*, Proc Natl Acad Sci U S A. 1997 Nov 11;94(23):12320-5; Seeger *et al.*, Biotechniques. 1997 Sep;23(3):512-7). U.S. Patent No. 5,700,922 discusses PNA-DNA-PNA chimeric molecules and their uses in diagnostics, modulating protein in organisms, and treatment of conditions susceptible to therapeutics.

Methods of characterizing the antisense binding properties of PNAs are discussed in Rose (Anal Chem. 1993 Dec 15;65(24):3545-9) and Jensen *et al.* (Biochemistry. 1997 Apr 22;36(16):5072-7). Rose uses capillary gel electrophoresis to determine binding of PNAs to their complementary oligonucleotide, measuring the relative binding kinetics and stoichiometry. Similar types of measurements were made by Jensen *et al.* using BIAcore™ technology.

Other applications of PNAs that have been described and will be apparent to the skilled artisan include use in DNA strand invasion, antisense inhibition, mutational analysis, enhancers of transcription, nucleic acid purification, isolation of transcriptionally active genes, blocking of transcription factor binding, genome cleavage, biosensors, *in situ* hybridization, and the like.

Polynucleotide Identification, Characterization and Expression

Polynucleotides compositions of the present invention may be identified, prepared and/or manipulated using any of a variety of well established techniques (see generally, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989, and other like references). For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.,* expression that is at least two fold greater in a tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed, for example, using the microarray technology of Affymetrix, Inc. (Santa Clara, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polynucleotides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as tumor cells.

Many template dependent processes are available to amplify a target sequences of interest present in a sample. One of the best known amplification methods is the polymerase chain reaction (PCR™) which is described in detail in U.S. Patent Nos. 4,683,195, 4,683,202 and 4,800,159, each of which is incorporated herein by reference in its entirety. Briefly, in PCR™, two primer sequences are prepared which are complementary to regions on opposite complementary strands of the target sequence. An excess of deoxynucleoside triphosphates is added to a reaction mixture along with a DNA polymerase (*e.g., Taq* polymerase). If the target sequence is present in a sample, the primers will bind to the target and the polymerase will cause the primers to be extended along the target sequence by adding on nucleotides. By raising and lowering the temperature of the reaction mixture, the extended primers will dissociate from the target to form reaction products, excess primers will bind to the target and to the reaction product and the process is repeated. Preferably reverse transcription and PCR™ amplification procedure may be performed in order to quantify the amount of mRNA amplified. Polymerase chain reaction methodologies are well known in the art.

Any of a number of other template dependent processes, many of which are variations of the PCR ™ amplification technique, are readily known and available in the art. Illustratively, some such methods include the ligase chain reaction (referred to as LCR), described, for example, in Eur. Pat. Appl. Publ. No. 320,308 and U.S. Patent No. 4,883,750; Qbeta Replicase, described in PCT Intl. Pat. Appl. Publ. No. PCT/US87/00880; Strand Displacement Amplification (SDA) and Repair Chain

Reaction (RCR). Still other amplification methods are described in Great Britain Pat. Appl. No. 2 202 328, and in PCT Intl. Pat. Appl. Publ. No. PCT/US89/01025. Other nucleic acid amplification procedures include transcription-based amplification systems (TAS) (PCT Intl. Pat. Appl. Publ. No. WO 88/10315), including nucleic acid sequence based amplification (NASBA) and 3SR. Eur. Pat. Appl. Publ. No. 329,822 describes a nucleic acid amplification process involving cyclically synthesizing single-stranded RNA ("ssRNA"), ssDNA, and double-stranded DNA (dsDNA). PCT Intl. Pat. Appl. Publ. No. WO 89/06700 describes a nucleic acid sequence amplification scheme based on the hybridization of a promoter/primer sequence to a target single-stranded DNA ("ssDNA") followed by transcription of many RNA copies of the sequence. Other amplification methods such as "RACE" (Frohman, 1990), and "one-sided PCR" (Ohara, 1989) are also well-known to those of skill in the art.

An amplified portion of a polynucleotide of the present invention may be used to isolate a full length gene from a suitable library (*e.g.,* a tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (*e.g.,* by nick-translation or end-labeling with ^{32}P) using well-known techniques. A bacterial or bacteriophage library is then generally screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (*see* Sambrook et al., *Molecular Cloning: A Laboratory Manual,* Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences can then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, amplification techniques, such as those described above, can be useful for obtaining a full length coding sequence from a partial cDNA sequence. One such amplification technique is inverse PCR (*see* Triglia et al., *Nucl. Acids Res.*

16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., *PCR Methods Applic. 1*:111-19, 1991) and walking PCR (Parker et al., *Nucl. Acids. Res. 19*:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (*e.g.,* NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

In other embodiments of the invention, polynucleotide sequences or fragments thereof which encode polypeptides of the invention, or fusion proteins or functional equivalents thereof, may be used in recombinant DNA molecules to direct expression of a polypeptide in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences that encode substantially the same or a functionally equivalent amino acid sequence may be produced and these sequences may be used to clone and express a given polypeptide.

As will be understood by those of skill in the art, it may be advantageous in some instances to produce polypeptide-encoding nucleotide sequences possessing non-naturally occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce a recombinant RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

Moreover, the polynucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter polypeptide encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the gene product. For example, DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. In addition, site-directed mutagenesis may be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, or introduce mutations, and so forth.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences may be ligated to a heterologous sequence to encode a fusion protein. For example, to screen peptide libraries for inhibitors of polypeptide activity, it may be useful to encode a chimeric protein that can be recognized by a commercially available antibody. A fusion protein may also be engineered to contain a cleavage site located between the polypeptide-encoding sequence and the heterologous protein sequence, so that the polypeptide may be cleaved and purified away from the heterologous moiety.

Sequences encoding a desired polypeptide may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers, M. H. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 215-223, Horn, T. et al. (1980) *Nucl. Acids Res. Symp. Ser.* 225-232). Alternatively, the protein itself may be produced using chemical methods to synthesize the amino acid sequence of a polypeptide, or a portion thereof. For example, peptide synthesis can be performed using various solid-phase techniques (Roberge, J. Y. et al. (1995) *Science 269*:202-204) and automated synthesis may be achieved, for example, using the ABI 431A Peptide Synthesizer (Perkin Elmer, Palo Alto, CA).

A newly synthesized peptide may be substantially purified by preparative high performance liquid chromatography (*e.g.*, Creighton, T. (1983) Proteins, Structures and Molecular Principles, WH Freeman and Co., New York, N.Y.) or other comparable techniques available in the art. The composition of the synthetic peptides may be confirmed by amino acid analysis or sequencing (*e.g.*, the Edman degradation procedure). Additionally, the amino acid sequence of a polypeptide, or any part thereof, may be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

In order to express a desired polypeptide, the nucleotide sequences encoding the polypeptide, or functional equivalents, may be inserted into appropriate

expression vector, *i.e.*, a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding a polypeptide of interest and appropriate transcriptional and translational control elements. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* genetic recombination. Such techniques are described, for example, in Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y., and Ausubel, F. M. et al. (1989) Current Protocols in Molecular Biology, John Wiley & Sons, New York. N.Y.

A variety of expression vector/host systems may be utilized to contain and express polynucleotide sequences. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (*e.g.*, baculovirus); plant cell systems transformed with virus expression vectors (*e.g.*, cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (*e.g.*, Ti or pBR322 plasmids); or animal cell systems.

The "control elements" or "regulatory sequences" present in an expression vector are those non-translated regions of the vector--enhancers, promoters, 5' and 3' untranslated regions--which interact with host cellular proteins to carry out transcription and translation. Such elements may vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, may be used. For example, when cloning in bacterial systems, inducible promoters such as the hybrid lacZ promoter of the PBLUESCRIPT phagemid (Stratagene, La Jolla, Calif.) or PSPORT1 plasmid (Gibco BRL, Gaithersburg, MD) and the like may be used. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are generally preferred. If it is necessary to generate a cell line that contains multiple copies of the sequence encoding a polypeptide, vectors based on SV40 or EBV may be advantageously used with an appropriate selectable marker.

In bacterial systems, any of a number of expression vectors may be selected depending upon the use intended for the expressed polypeptide. For example, when large quantities are needed, for example for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified may be used. Such vectors include, but are not limited to, the multifunctional *E. coli* cloning

and expression vectors such as BLUESCRIPT (Stratagene), in which the sequence encoding the polypeptide of interest may be ligated into the vector in frame with sequences for the amino-terminal Met and the subsequent 7 residues of .beta.-galactosidase so that a hybrid protein is produced; pIN vectors (Van Heeke, G. and S. M. Schuster (1989) *J. Biol. Chem. 264*:5503-5509); and the like. pGEX Vectors (Promega, Madison, Wis.) may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione-agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems may be designed to include heparin, thrombin, or factor XA protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast, Saccharomyces cerevisiae, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH may be used. For reviews, see Ausubel et al. (supra) and Grant et al. (1987) *Methods Enzymol.* 153:516-544.

In cases where plant expression vectors are used, the expression of sequences encoding polypeptides may be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV may be used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) *EMBO J. 6*:307-311. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used (Coruzzi, G. et al. (1984) *EMBO J. 3*:1671-1680; Broglie, R. et al. (1984) *Science 224*:838-843; and Winter, J. et al. (1991) *Results Probl. Cell Differ. 17*:85-105). These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (see, for example, Hobbs, S. or Murry, L. E. in McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York, N.Y.; pp. 191-196).

An insect system may also be used to express a polypeptide of interest. For example, in one such system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in Spodoptera frugiperda cells or in Trichoplusia larvae. The sequences encoding the polypeptide may be cloned into a non-essential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of the polypeptide-encoding sequence will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses may then be used to infect, for example, S. frugiperda

cells or Trichoplusia larvae in which the polypeptide of interest may be expressed (Engelhard, E. K. et al. (1994) *Proc. Natl. Acad. Sci. 91* :3224-3227).

In mammalian host cells, a number of viral-based expression systems are generally available. For example, in cases where an adenovirus is used as an expression vector, sequences encoding a polypeptide of interest may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain a viable virus which is capable of expressing the polypeptide in infected host cells (Logan, J. and Shenk, T. (1984) *Proc. Natl. Acad. Sci. 81*:3655-3659). In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells.

Specific initiation signals may also be used to achieve more efficient translation of sequences encoding a polypeptide of interest. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding the polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a portion thereof, is inserted, exogenous translational control signals including the ATG initiation codon should be provided. Furthermore, the initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used, such as those described in the literature (Scharf, D. et al. (1994) *Results Probl. Cell Differ. 20*:125-162).

In addition, a host cell strain may be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation. glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" form of the protein may also be used to facilitate correct insertion, folding and/or function. Different host cells such as CHO, COS, HeLa, MDCK, HEK293, and WI38, which have specific cellular machinery and characteristic mechanisms for such post-translational activities, may be chosen to ensure the correct modification and processing of the foreign protein.

For long-term, high-yield production of recombinant proteins, stable expression is generally preferred. For example, cell lines which stably express a polynucleotide of interest may be transformed using expression vectors which may

contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be proliferated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler, M. et al. (1977) *Cell 11*:223-32) and adenine phosphoribosyltransferase (Lowy, I. et al. (1990) *Cell 22*:817-23) genes which can be employed in tk.sup.- or aprt.sup.- cells, respectively. Also, antimetabolite, antibiotic or herbicide resistance can be used as the basis for selection; for example, dhfr which confers resistance to methotrexate (Wigler, M. et al. (1980) *Proc. Natl. Acad. Sci. 77*:3567-70); npt, which confers resistance to the aminoglycosides, neomycin and G-418 (Colbere-Garapin, F. et al (1981) *J. Mol. Biol. 150*:1-14); and als or pat, which confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively (Murry, *supra*). Additional selectable genes have been described, for example, trpB, which allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine (Hartman, S. C. and R. C. Mulligan (1988) *Proc. Natl. Acad. Sci. 85*:8047-51). The use of visible markers has gained popularity with such markers as anthocyanins, beta-glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, being widely used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system (Rhodes, C. A. et al. (1995) *Methods Mol. Biol. 55*:121-131).

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, its presence and expression may need to be confirmed. For example, if the sequence encoding a polypeptide is inserted within a marker gene sequence, recombinant cells containing sequences can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a polypeptide-encoding sequence under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

Alternatively, host cells that contain and express a desired polynucleotide sequence may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-

RNA hybridizations and protein bioassay or immunoassay techniques which include, for example, membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein.

A variety of protocols for detecting and measuring the expression of polynucleotide-encoded products, using either polyclonal or monoclonal antibodies specific for the product are known in the art. Examples include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on a given polypeptide may be preferred for some applications, but a competitive binding assay may also be employed. These and other assays are described, among other places, in Hampton, R. et al. (1990; Serological Methods, a Laboratory Manual, APS Press, St Paul. Minn.) and Maddox, D. E. et al. (1983; *J. Exp. Med. 158*:1211-1216).

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides include oligolabeling, nick translation, end-labeling or PCR amplification using a labeled nucleotide. Alternatively, the sequences, or any portions thereof may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits. Suitable reporter molecules or labels, which may be used include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with a polynucleotide sequence of interest may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a recombinant cell may be secreted or contained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides of the invention may be designed to contain signal sequences which direct secretion of the encoded polypeptide through a prokaryotic or eukaryotic cell membrane. Other recombinant constructions may be used to join sequences encoding a polypeptide of interest to nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow

purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). The inclusion of cleavable linker sequences such as those specific for Factor XA or enterokinase (Invitrogen. San Diego, Calif.) between the purification domain and the encoded polypeptide may be used to facilitate purification. One such expression vector provides for expression of a fusion protein containing a polypeptide of interest and a nucleic acid encoding 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification on IMIAC (immobilized metal ion affinity chromatography) as described in Porath, J. et al. (1992, *Prot. Exp. Purif. 3*:263-281) while the enterokinase cleavage site provides a means for purifying the desired polypeptide from the fusion protein. A discussion of vectors which contain fusion proteins is provided in Kroll, D. J. et al. (1993; *DNA Cell Biol. 12*:441-453).

In addition to recombinant production methods, polypeptides of the invention, and fragments thereof, may be produced by direct peptide synthesis using solid-phase techniques (Merrifield J. (1963) *J. Am. Chem. Soc. 85*:2149-2154). Protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Alternatively, various fragments may be chemically synthesized separately and combined using chemical methods to produce the full length molecule.

Antibody Compositions, Fragments Thereof and Other Binding Agents

According to another aspect, the present invention further provides binding agents, such as antibodies and antigen-binding fragments thereof, that exhibit immunological binding to a tumor polypeptide disclosed herein, or to a portion, variant or derivative thereof. An antibody, or antigen-binding fragment thereof, is said to "specifically bind," "immunogically bind," and/or is "immunologically reactive" to a polypeptide of the invention if it reacts at a detectable level (within, for example, an ELISA assay) with the polypeptide, and does not react detectably with unrelated polypeptides under similar conditions.

Immunological binding, as used in this context, generally refers to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater

affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and on geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. The ratio of K_{off}/K_{on} enables cancellation of all parameters not related to affinity, and is thus equal to the dissociation constant K_d. See, generally, Davies et al. (1990) Annual Rev. Biochem. 59:439-473.

An "antigen-binding site," or "binding portion" of an antibody refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains are referred to as "hypervariable regions" which are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus the term "FR" refers to amino acid sequences which are naturally found between and adjacent to hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs."

Binding agents may be further capable of differentiating between patients with and without a cancer, such as lung cancer, using the representative assays provided herein. For example, antibodies or other binding agents that bind to a tumor protein will preferably generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, more preferably at least about 30% of patients. Alternatively, or in addition, the antibody will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (*e.g.*, blood, sera, sputum, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. Preferably, a statistically significant number of samples with and without the disease will be assayed. Each

binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. *See, e.g.,* Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (*e.g.,* mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, *Eur. J. Immunol. 6*:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (*i.e.*, reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks,

colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

A number of therapeutically useful molecules are known in the art which comprise antigen-binding sites that are capable of exhibiting immunological binding properties of an antibody molecule. The proteolytic enzyme papain preferentially cleaves IgG molecules to yield several fragments, two of which (the "F(ab)" fragments) each comprise a covalent heterodimer that includes an intact antigen-binding site. The enzyme pepsin is able to cleave IgG molecules to provide several fragments, including the "$F(ab')_2$ " fragment which comprises both antigen-binding sites. An "Fv" fragment can be produced by preferential proteolytic cleavage of an IgM, and on rare occasions IgG or IgA immunoglobulin molecule. Fv fragments are, however, more commonly derived using recombinant techniques known in the art. The Fv fragment includes a non-covalent $V_H::V_L$ heterodimer including an antigen-binding site which retains much of the antigen recognition and binding capabilities of the native antibody molecule. Inbar et al. (1972) Proc. Nat. Acad. Sci. USA 69:2659-2662; Hochman et al. (1976) Biochem 15:2706-2710; and Ehrlich et al. (1980) Biochem 19:4091-4096.

A single chain Fv ("sFv") polypeptide is a covalently linked $V_H::V_L$ heterodimer which is expressed from a gene fusion including V_H- and V_L-encoding genes linked by a peptide-encoding linker. Huston et al. (1988) Proc. Nat. Acad. Sci. USA 85(16):5879-5883. A number of methods have been described to discern chemical structures for converting the naturally aggregated--but chemically separated--light and heavy polypeptide chains from an antibody V region into an sFv molecule which will fold into a three dimensional structure substantially similar to the structure of an antigen-binding site. See, *e.g.*, U.S. Pat. Nos. 5,091,513 and 5,132,405, to Huston et al.; and U.S. Pat. No. 4,946,778, to Ladner et al.

Each of the above-described molecules includes a heavy chain and a light chain CDR set, respectively interposed between a heavy chain and a light chain FR

set which provide support to the CDRS and define the spatial relationship of the CDRs relative to each other. As used herein, the term "CDR set" refers to the three hypervariable regions of a heavy or light chain V region. Proceeding from the N-terminus of a heavy or light chain, these regions are denoted as "CDR1," "CDR2," and "CDR3" respectively. An antigen-binding site, therefore, includes six CDRs, comprising the CDR set from each of a heavy and a light chain V region. A polypeptide comprising a single CDR, (*e.g.*, a CDR1, CDR2 or CDR3) is referred to herein as a "molecular recognition unit." Crystallographic analysis of a number of antigen-antibody complexes has demonstrated that the amino acid residues of CDRs form extensive contact with bound antigen, wherein the most extensive antigen contact is with the heavy chain CDR3. Thus, the molecular recognition units are primarily responsible for the specificity of an antigen-binding site.

As used herein, the term "FR set" refers to the four flanking amino acid sequences which frame the CDRs of a CDR set of a heavy or light chain V region. Some FR residues may contact bound antigen; however, FRs are primarily responsible for folding the V region into the antigen-binding site, particularly the FR residues directly adjacent to the CDRS. Within FRs, certain amino residues and certain structural features are very highly conserved. In this regard, all V region sequences contain an internal disulfide loop of around 90 amino acid residues. When the V regions fold into a binding-site, the CDRs are displayed as projecting loop motifs which form an antigen-binding surface. It is generally recognized that there are conserved structural regions of FRs which influence the folded shape of the CDR loops into certain "canonical" structures--regardless of the precise CDR amino acid sequence. Further, certain FR residues are known to participate in non-covalent interdomain contacts which stabilize the interaction of the antibody heavy and light chains.

A number of "humanized" antibody molecules comprising an antigen-binding site derived from a non-human immunoglobulin have been described, including chimeric antibodies having rodent V regions and their associated CDRs fused to human constant domains (Winter et al. (1991) Nature 349:293-299; Lobuglio et al. (1989) Proc. Nat. Acad. Sci. USA 86:4220-4224; Shaw et al. (1987) J Immunol. 138:4534-4538; and Brown et al. (1987) Cancer Res. 47:3577-3583), rodent CDRs grafted into a human supporting FR prior to fusion with an appropriate human antibody constant domain (Riechmann et al. (1988) Nature 332:323-327; Verhoeyen et al. (1988) Science 239:1534-1536; and Jones et al. (1986) Nature 321:522-525), and rodent CDRs supported by recombinantly veneered rodent FRs (European Patent Publication No. 519,596, published Dec. 23, 1992). These "humanized" molecules are designed to

minimize unwanted immunological response toward rodent antihuman antibody molecules which limits the duration and effectiveness of therapeutic applications of those moieties in human recipients.

As used herein, the terms "veneered FRs" and "recombinantly veneered FRs" refer to the selective replacement of FR residues from, *e.g.*, a rodent heavy or light chain V region, with human FR residues in order to provide a xenogeneic molecule comprising an antigen-binding site which retains substantially all of the native FR polypeptide folding structure. Veneering techniques are based on the understanding that the ligand binding characteristics of an antigen-binding site are determined primarily by the structure and relative disposition of the heavy and light chain CDR sets within the antigen-binding surface. Davies et al. (1990) Ann. Rev. Biochem. 59:439-473. Thus, antigen binding specificity can be preserved in a humanized antibody only wherein the CDR structures, their interaction with each other, and their interaction with the rest of the V region domains are carefully maintained. By using veneering techniques, exterior (*e.g.*, solvent-accessible) FR residues which are readily encountered by the immune system are selectively replaced with human residues to provide a hybrid molecule that comprises either a weakly immunogenic, or substantially non-immunogenic veneered surface.

The process of veneering makes use of the available sequence data for human antibody variable domains compiled by Kabat et al., in Sequences of Proteins of Immunological Interest, 4th ed., (U.S. Dept. of Health and Human Services, U.S. Government Printing Office, 1987), updates to the Kabat database, and other accessible U.S. and foreign databases (both nucleic acid and protein). Solvent accessibilities of V region amino acids can be deduced from the known three-dimensional structure for human and murine antibody fragments. There are two general steps in veneering a murine antigen-binding site. Initially, the FRs of the variable domains of an antibody molecule of interest are compared with corresponding FR sequences of human variable domains obtained from the above-identified sources. The most homologous human V regions are then compared residue by residue to corresponding murine amino acids. The residues in the murine FR which differ from the human counterpart are replaced by the residues present in the human moiety using recombinant techniques well known in the art. Residue switching is only carried out with moieties which are at least partially exposed (solvent accessible), and care is exercised in the replacement of amino acid residues which may have a significant effect on the tertiary structure of V region domains, such as proline, glycine and charged amino acids.

In this manner, the resultant "veneered" murine antigen-binding sites are thus designed to retain the murine CDR residues, the residues substantially adjacent to the CDRs, the residues identified as buried or mostly buried (solvent inaccessible), the residues believed to participate in non-covalent (*e.g.*, electrostatic and hydrophobic) contacts between heavy and light chain domains, and the residues from conserved structural regions of the FRs which are believed to influence the "canonical" tertiary structures of the CDR loops. These design criteria are then used to prepare recombinant nucleotide sequences which combine the CDRs of both the heavy and light chain of a murine antigen-binding site into human-appearing FRs that can be used to transfect mammalian cells for the expression of recombinant human antibodies which exhibit the antigen specificity of the murine antibody molecule.

In another embodiment of the invention, monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ^{90}Y, ^{123}I, ^{125}I, ^{131}I, ^{186}Re, ^{188}Re, ^{211}At, and ^{212}Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (*e.g.*, covalently bonded) to a suitable monoclonal antibody either directly or indirectly (*e.g.*, via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (*e.g.*, a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker

group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, *e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (*e.g.*, U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (*e.g.*, U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (*e.g.*, U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (*e.g.*, U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (*e.g.*, U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers that provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (*e.g.*, U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (*e.g.*, U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (*e.g.*, U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

T Cell Compositions

The present invention, in another aspect, provides T cells specific for a tumor polypeptide disclosed herein, or for a variant or derivative thereof. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the Isolex™ System, available from Nexell Therapeutics, Inc. (Irvine, CA; see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a polypeptide, polynucleotide encoding a polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide of interest. Preferably, a tumor polypeptide or polynucleotide of the invention is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., *Cancer Res.* *54*:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (*e.g.*, by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days will typically result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (*e.g.*, TNF or IFN-γ) is indicative of T cell activation (*see* Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a tumor polypeptide, polynucleotide or polypeptide-expressing APC may be $CD4^+$ and/or $CD8^+$. Tumor polypeptide-specific T

cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from a patient, a related donor or an unrelated donor, and are administered to the patient following stimulation and expansion.

For therapeutic purposes, $CD4^+$ or $CD8^+$ T cells that proliferate in response to a tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of the tumor polypeptide can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

Pharmaceutical Compositions

In additional embodiments, the present invention concerns formulation of one or more of the polynucleotide, polypeptide, T-cell and/or antibody compositions disclosed herein in pharmaceutically-acceptable carriers for administration to a cell or an animal, either alone, or in combination with one or more other modalities of therapy.

It will be understood that, if desired, a composition as disclosed herein may be administered in combination with other agents as well, such as, *e.g.*, other proteins or polypeptides or various pharmaceutically-active agents. In fact, there is virtually no limit to other components that may also be included, given that the additional agents do not cause a significant adverse effect upon contact with the target cells or host tissues. The compositions may thus be delivered along with various other agents as required in the particular instance. Such compositions may be purified from host cells or other biological sources, or alternatively may be chemically synthesized as described herein. Likewise, such compositions may further comprise substituted or derivatized RNA or DNA compositions.

Therefore, in another aspect of the present invention, pharmaceutical compositions are provided comprising one or more of the polynucleotide, polypeptide, antibody, and/or T-cell compositions described herein in combination with a physiologically acceptable carrier. In certain preferred embodiments, the pharmaceutical compositions of the invention comprise immunogenic polynucleotide and/or polypeptide compositions of the invention for use in prophylactic and theraputic vaccine applications. Vaccine preparation is generally described in, for example, M.F.

Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Generally, such compositions will comprise one or more polynucleotide and/or polypeptide compositions of the present invention in combination with one or more immunostimulants.

It will be apparent that any of the pharmaceutical compositions described herein can contain pharmaceutically acceptable salts of the polynucleotides and polypeptides of the invention. Such salts can be prepared, for example, from pharmaceutically acceptable non-toxic bases, including organic bases (*e.g.*, salts of primary, secondary and tertiary amines and basic amino acids) and inorganic bases (*e.g.*, sodium, potassium, lithium, ammonium, calcium and magnesium salts).

In another embodiment, illustrative immunogenic compositions, *e.g.*, vaccine compositions, of the present invention comprise DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated *in situ*. As noted above, the polynucleotide may be administered within any of a variety of delivery systems known to those of ordinary skill in the art. Indeed, numerous gene delivery techniques are well known in the art, such as those described by Rolland, *Crit. Rev. Therap. Drug Carrier Systems 15*:143-198, 1998, and references cited therein. Appropriate polynucleotide expression systems will, of course, contain the necessary regulatory DNA regulatory sequences for expression in a patient (such as a suitable promoter and terminating signal). Alternatively, bacterial delivery systems may involve the administration of a bacterium (such as *Bacillus-Calmette-Guerrin*) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope.

Therefore, in certain embodiments, polynucleotides encoding immunogenic polypeptides described herein are introduced into suitable mammalian host cells for expression using any of a number of known viral-based systems. In one illustrative embodiment, retroviruses provide a convenient and effective platform for gene delivery systems. A selected nucleotide sequence encoding a polypeptide of the present invention can be inserted into a vector and packaged in retroviral particles using techniques known in the art. The recombinant virus can then be isolated and delivered to a subject. A number of illustrative retroviral systems have been described (*e.g.*, U.S. Pat. No. 5,219,740; Miller and Rosman (1989) BioTechniques 7:980-990; Miller, A. D. (1990) Human Gene Therapy 1:5-14; Scarpa et al. (1991) Virology 180:849-852; Burns et al. (1993) Proc. Natl. Acad. Sci. USA 90:8033-8037; and Boris-Lawrie and Temin (1993) Cur. Opin. Genet. Develop. 3:102-109.

In addition, a number of illustrative adenovirus-based systems have also been described. Unlike retroviruses which integrate into the host genome, adenoviruses

persist extrachromosomally thus minimizing the risks associated with insertional mutagenesis (Haj-Ahmad and Graham (1986) J. Virol. 57:267-274; Bett et al. (1993) J. Virol. 67:5911-5921; Mittereder et al. (1994) Human Gene Therapy 5:717-729; Seth et al. (1994) J. Virol. 68:933-940; Barr et al. (1994) Gene Therapy 1:51-58; Berkner, K. L. (1988) BioTechniques 6:616-629; and Rich et al. (1993) Human Gene Therapy 4:461-476).

Various adeno-associated virus (AAV) vector systems have also been developed for polynucleotide delivery. AAV vectors can be readily constructed using techniques well known in the art. See, *e.g.*, U.S. Pat. Nos. 5,173,414 and 5,139,941; International Publication Nos. WO 92/01070 and WO 93/03769; Lebkowski et al. (1988) Molec. Cell. Biol. 8:3988-3996; Vincent et al. (1990) Vaccines 90 (Cold Spring Harbor Laboratory Press); Carter, B. J. (1992) Current Opinion in Biotechnology 3:533-539; Muzyczka, N. (1992) Current Topics in Microbiol. and Immunol. 158:97-129; Kotin, R. M. (1994) Human Gene Therapy 5:793-801; Shelling and Smith (1994) Gene Therapy 1:165-169; and Zhou et al. (1994) J. Exp. Med. 179:1867-1875.

Additional viral vectors useful for delivering the polynucleotides encoding polypeptides of the present invention by gene transfer include those derived from the pox family of viruses, such as vaccinia virus and avian poxvirus. By way of example, vaccinia virus recombinants expressing the novel molecules can be constructed as follows. The DNA encoding a polypeptide is first inserted into an appropriate vector so that it is adjacent to a vaccinia promoter and flanking vaccinia DNA sequences, such as the sequence encoding thymidine kinase (TK). This vector is then used to transfect cells which are simultaneously infected with vaccinia. Homologous recombination serves to insert the vaccinia promoter plus the gene encoding the polypeptide of interest into the viral genome. The resulting TK.sup.(-) recombinant can be selected by culturing the cells in the presence of 5-bromodeoxyuridine and picking viral plaques resistant thereto.

A vaccinia-based infection/transfection system can be conveniently used to provide for inducible, transient expression or coexpression of one or more polypeptides described herein in host cells of an organism. In this particular system, cells are first infected in vitro with a vaccinia virus recombinant that encodes the bacteriophage T7 RNA polymerase. This polymerase displays exquisite specificity in that it only transcribes templates bearing T7 promoters. Following infection, cells are transfected with the polynucleotide or polynucleotides of interest, driven by a T7 promoter. The polymerase expressed in the cytoplasm from the vaccinia virus recombinant transcribes the transfected DNA into RNA which is then translated into

polypeptide by the host translational machinery. The method provides for high level, transient, cytoplasmic production of large quantities of RNA and its translation products. See, *e.g.*, Elroy-Stein and Moss, Proc. Natl. Acad. Sci. USA (1990) 87:6743-6747; Fuerst et al. Proc. Natl. Acad. Sci. USA (1986) 83:8122-8126.

Alternatively, avipoxviruses, such as the fowlpox and canarypox viruses, can also be used to deliver the coding sequences of interest. Recombinant avipox viruses, expressing immunogens from mammalian pathogens, are known to confer protective immunity when administered to non-avian species. The use of an Avipox vector is particularly desirable in human and other mammalian species since members of the Avipox genus can only productively replicate in susceptible avian species and therefore are not infective in mammalian cells. Methods for producing recombinant Avipoxviruses are known in the art and employ genetic recombination, as described above with respect to the production of vaccinia viruses. See, *e.g.*, WO 91/12882; WO 89/03429; and WO 92/03545.

Any of a number of alphavirus vectors can also be used for delivery of polynucleotide compositions of the present invention, such as those vectors described in U.S. Patent Nos. 5,843,723; 6,015,686; 6,008,035 and 6,015,694. Certain vectors based on Venezuelan Equine Encephalitis (VEE) can also be used, illustrative examples of which can be found in U.S. Patent Nos. 5,505,947 and 5,643,576.

Moreover, molecular conjugate vectors, such as the adenovirus chimeric vectors described in Michael et al. J. Biol. Chem. (1993) 268:6866-6869 and Wagner et al. Proc. Natl. Acad. Sci. USA (1992) 89:6099-6103, can also be used for gene delivery under the invention.

Additional illustrative information on these and other known viral-based delivery systems can be found, for example, in Fisher-Hoch et al., *Proc. Natl. Acad. Sci. USA 86*:317-321, 1989; Flexner et al., *Ann. N.Y. Acad. Sci. 569*:86-103, 1989; Flexner et al., *Vaccine 8*:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques 6*:616-627, 1988; Rosenfeld et al., *Science 252*:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA 91*:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA 90*:11498-11502, 1993; Guzman et al., *Circulation 88*:2838-2848, 1993; and Guzman et al., *Cir. Res. 73*:1202-1207, 1993.

In certain embodiments, a polynucleotide may be integrated into the genome of a target cell. This integration may be in the specific location and orientation *via* homologous recombination (gene replacement) or it may be integrated in a random, non-specific location (gene augmentation). In yet further embodiments, the

polynucleotide may be stably maintained in the cell as a separate, episomal segment of DNA. Such polynucleotide segments or "episomes" encode sequences sufficient to permit maintenance and replication independent of or in synchronization with the host cell cycle. The manner in which the expression construct is delivered to a cell and where in the cell the polynucleotide remains is dependent on the type of expression construct employed.

In another embodiment of the invention, a polynucleotide is administered/delivered as "naked" DNA, for example as described in Ulmer et al., *Science 259*:1745-1749, 1993 and reviewed by Cohen, *Science 259*:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

In still another embodiment, a composition of the present invention can be delivered via a particle bombardment approach, many of which have been described. In one illustrative example, gas-driven particle acceleration can be achieved with devices such as those manufactured by Powderject Pharmaceuticals PLC (Oxford, UK) and Powderject Vaccines Inc. (Madison, WI), some examples of which are described in U.S. Patent Nos. 5,846,796; 6,010,478; 5,865,796; 5,584,807; and EP Patent No. 0500 799. This approach offers a needle-free delivery approach wherein a dry powder formulation of microscopic particles, such as polynucleotide or polypeptide particles, are accelerated to high speed within a helium gas jet generated by a hand held device, propelling the particles into a target tissue of interest.

In a related embodiment, other devices and methods that may be useful for gas-driven needle-less injection of compositions of the present invention include those provided by Bioject, Inc. (Portland, OR), some examples of which are described in U.S. Patent Nos. 4,790,824; 5,064,413; 5,312,335; 5,383,851; 5,399,163; 5,520,639 and 5,993,412.

According to another embodiment, the pharmaceutical compositions described herein will comprise one or more immunostimulants in addition to the immunogenic polynucleotide, polypeptide, antibody, T-cell and/or APC compositions of this invention. An immunostimulant refers to essentially any substance that enhances or potentiates an immune response (antibody and/or cell-mediated) to an exogenous antigen. One preferred type of immunostimulant comprises an adjuvant. Many adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, *Bortadella pertussis* or *Mycobacterium tuberculosis* derived proteins. Certain adjuvants are commercially available as, for example, Freund's Incomplete

Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); AS-2 (SmithKline Beecham, Philadelphia, PA); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF, interleukin-2, -7, -12, and other like growth factors, may also be used as adjuvants.

Within certain embodiments of the invention, the adjuvant composition is preferably one that induces an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (*e.g.,* IFN-γ, TNFα, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (*e.g.,* IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, *Ann. Rev. Immunol.* 7:145-173, 1989.

Certain preferred adjuvants for eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A, together with an aluminum salt. MPL® adjuvants are available from Corixa Corporation (Seattle, WA; *see*, for example, US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555, WO 99/33488 and U.S. Patent Nos. 6,008,200 and 5,856,462. Immunostimulatory DNA sequences are also described, for example, by Sato et al., *Science 273*:352, 1996. Another preferred adjuvant comprises a saponin, such as Quil A, or derivatives thereof, including QS21 and QS7 (Aquila Biopharmaceuticals Inc., Framingham, MA); Escin; Digitonin; or *Gypsophila* or *Chenopodium quinoa* saponins . Other preferred formulations include more than one saponin in the adjuvant combinations of the present invention, for example combinations of at least two of the following group comprising QS21, QS7, Quil A, β-escin, or digitonin.

Alternatively the saponin formulations may be combined with vaccine vehicles composed of chitosan or other polycationic polymers, polylactide and polylactide-co-glycolide particles, poly-N-acetyl glucosamine-based polymer matrix, particles composed of polysaccharides or chemically modified polysaccharides, liposomes and lipid-based particles, particles composed of glycerol monoesters, etc. The saponins may also be formulated in the presence of cholesterol to form particulate structures such as liposomes or ISCOMs. Furthermore, the saponins may be formulated together with a polyoxyethylene ether or ester, in either a non-particulate solution or suspension, or in a particulate structure such as a paucilamelar liposome or ISCOM. The saponins may also be formulated with excipients such as Carbopol^{R} to increase viscosity, or may be formulated in a dry powder form with a powder excipient such as lactose.

In one preferred embodiment, the adjuvant system includes the combination of a monophosphoryl lipid A and a saponin derivative, such as the combination of QS21 and 3D-MPL® adjuvant, as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprise an oil-in-water emulsion and tocopherol. Another particularly preferred adjuvant formulation employing QS21, 3D-MPL® adjuvant and tocopherol in an oil-in-water emulsion is described in WO 95/17210.

Another enhanced adjuvant system involves the combination of a CpG-containing oligonucleotide and a saponin derivative particularly the combination of CpG and QS21 is disclosed in WO 00/09159. Preferably the formulation additionally comprises an oil in water emulsion and tocopherol.

Additional illustrative adjuvants for use in the pharmaceutical compositions of the invention include Montanide ISA 720 (Seppic, France), SAF (Chiron, California, United States), ISCOMS (CSL), MF-59 (Chiron), the SBAS series of adjuvants (*e.g.,* SBAS-2 or SBAS-4, available from SmithKline Beecham, Rixensart, Belgium), Detox (Enhanzyn®) (Corixa, Hamilton, MT), RC-529 (Corixa, Hamilton, MT) and other aminoalkyl glucosaminide 4-phosphates (AGPs), such as those described in pending U.S. Patent Application Serial Nos. 08/853,826 and 09/074,720, the disclosures of which are incorporated herein by reference in their entireties, and polyoxyethylene ether adjuvants such as those described in WO 99/52549A1.

Other preferred adjuvants include adjuvant molecules of the general formula

(I): $HO(CH_2CH_2O)_n$-A-R,

wherein, n is 1-50, A is a bond or –C(O)-, R is C_{1-50} alkyl or Phenyl C_{1-50} alkyl.

One embodiment of the present invention consists of a vaccine formulation comprising a polyoxyethylene ether of general formula (I), wherein *n* is between 1 and 50, preferably 4-24, most preferably 9; the *R* component is C_{1-50}, preferably C_4-C_{20} alkyl and most preferably C_{12} alkyl, and *A* is a bond. The concentration of the polyoxyethylene ethers should be in the range 0.1-20%, preferably from 0.1-10%, and most preferably in the range 0.1-1%. Preferred polyoxyethylene ethers are selected from the following group: polyoxyethylene-9-lauryl ether, polyoxyethylene-9-steoryl ether, polyoxyethylene-8-steoryl ether, polyoxyethylene-4-lauryl ether, polyoxyethylene-35-lauryl ether, and polyoxyethylene-23-lauryl ether. Polyoxyethylene ethers such as polyoxyethylene lauryl ether are described in the Merck index (12^{th} edition: entry 7717). These adjuvant molecules are described in WO 99/52549.

The polyoxyethylene ether according to the general formula (I) above may, if desired, be combined with another adjuvant. For example, a preferred adjuvant combination is preferably with CpG as described in the pending UK patent application GB 9820956.2.

According to another embodiment of this invention, an immunogenic composition described herein is delivered to a host via antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-

surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcγ receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (*e.g.,* CD54 and CD11) and costimulatory molecules (*e.g.,* CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide of the invention (or portion or other variant thereof) such that the encoded polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place *ex vivo*, and a pharmaceutical composition comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs *in vivo*. *In vivo* and *ex vivo* transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., *Immunology and cell Biology 75*:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or

progenitor cells with the tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (*e.g.,* vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (*e.g.,* a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will typically vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, mucosal, intravenous, intracranial, intraperitoneal, subcutaneous and intramuscular administration.

Carriers for use within such pharmaceutical compositions are biocompatible, and may also be biodegradable. In certain embodiments, the formulation preferably provides a relatively constant level of active component release. In other embodiments, however, a more rapid rate of release immediately upon administration may be desired. The formulation of such compositions is well within the level of ordinary skill in the art using known techniques. Illustrative carriers useful in this regard include microparticles of poly(lactide-co-glycolide), polyacrylate, latex, starch, cellulose, dextran and the like. Other illustrative delayed-release carriers include supramolecular biovectors, which comprise a non-liquid hydrophilic core (*e.g.,* a cross-linked polysaccharide or oligosaccharide) and, optionally, an external layer comprising an amphiphilic compound, such as a phospholipid (*see e.g.,* U.S. Patent No. 5,151,254 and PCT applications WO 94/20078, WO/94/23701 and WO 96/06638). The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

In another illustrative embodiment, biodegradable microspheres (*e.g.,* polylactate polyglycolate) are employed as carriers for the compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268; 5,075,109; 5,928,647; 5,811,128; 5,820,883; 5,853,763; 5,814,344, 5,407,609 and 5,942,252. Modified hepatitis B core protein carrier systems. such as described in WO/99 40934, and references cited therein, will also be useful for many applications. Another illustrative carrier/delivery system employs a carrier comprising particulate-protein complexes, such as those described in U.S. Patent No.

5,928,647, which are capable of inducing a class I-restricted cytotoxic T lymphocyte responses in a host.

The pharmaceutical compositions of the invention will often further comprise one or more buffers (*e.g.,* neutral buffered saline or phosphate buffered saline), carbohydrates (*e.g.,* glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, bacteriostats, chelating agents such as EDTA or glutathione, adjuvants (*e.g.*, aluminum hydroxide), solutes that render the formulation isotonic, hypotonic or weakly hypertonic with the blood of a recipient, suspending agents, thickening agents and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate.

The pharmaceutical compositions described herein may be presented in unit-dose or multi-dose containers, such as sealed ampoules or vials. Such containers are typically sealed in such a way to preserve the sterility and stability of the formulation until use. In general, formulations may be stored as suspensions, solutions or emulsions in oily or aqueous vehicles. Alternatively, a pharmaceutical composition may be stored in a freeze-dried condition requiring only the addition of a sterile liquid carrier immediately prior to use.

The development of suitable dosing and treatment regimens for using the particular compositions described herein in a variety of treatment regimens, including *e.g.,* oral, parenteral, intravenous, intranasal, and intramuscular administration and formulation, is well known in the art, some of which are briefly discussed below for general purposes of illustration.

In certain applications, the pharmaceutical compositions disclosed herein may be delivered *via* oral administration to an animal. As such, these compositions may be formulated with an inert diluent or with an assimilable edible carrier, or they may be enclosed in hard- or soft-shell gelatin capsule, or they may be compressed into tablets, or they may be incorporated directly with the food of the diet.

The active compounds may even be incorporated with excipients and used in the form of ingestible tablets, buccal tables, troches, capsules, elixirs, suspensions, syrups, wafers, and the like (see, for example, Mathiowitz *et al.*, Nature 1997 Mar 27;386(6623):410-4; Hwang *et al.*, Crit Rev Ther Drug Carrier Syst 1998;15(3):243-84; U. S. Patent 5,641,515; U. S. Patent 5,580,579 and U. S. Patent 5,792,451). Tablets, troches, pills, capsules and the like may also contain any of a variety of additional components, for example, a binder, such as gum tragacanth, acacia, cornstarch, or gelatin; excipients, such as dicalcium phosphate; a disintegrating agent, such as corn starch, potato starch, alginic acid and the like; a lubricant, such as

magnesium stearate; and a sweetening agent, such as sucrose, lactose or saccharin may be added or a flavoring agent, such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar, or both. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compounds may be incorporated into sustained-release preparation and formulations.

Typically, these formulations will contain at least about 0.1% of the active compound or more, although the percentage of the active ingredient(s) may, of course, be varied and may conveniently be between about 1 or 2% and about 60% or 70% or more of the weight or volume of the total formulation. Naturally, the amount of active compound(s) in each therapeutically useful composition may be prepared is such a way that a suitable dosage will be obtained in any given unit dose of the compound. Factors such as solubility, bioavailability, biological half-life, route of administration, product shelf life, as well as other pharmacological considerations will be contemplated by one skilled in the art of preparing such pharmaceutical formulations, and as such, a variety of dosages and treatment regimens may be desirable.

For oral administration the compositions of the present invention may alternatively be incorporated with one or more excipients in the form of a mouthwash, dentifrice, buccal tablet, oral spray, or sublingual orally-administered formulation. Alternatively, the active ingredient may be incorporated into an oral solution such as one containing sodium borate, glycerin and potassium bicarbonate, or dispersed in a dentifrice, or added in a therapeutically-effective amount to a composition that may include water, binders, abrasives, flavoring agents, foaming agents, and humectants. Alternatively the compositions may be fashioned into a tablet or solution form that may be placed under the tongue or otherwise dissolved in the mouth.

In certain circumstances it will be desirable to deliver the pharmaceutical compositions disclosed herein parenterally, intravenously, intramuscularly, or even intraperitoneally. Such approaches are well known to the skilled artisan, some of which are further described, for example, in U. S. Patent 5,543,158; U. S. Patent 5,641,515 and U. S. Patent 5,399,363. In certain embodiments, solutions of the active compounds as free base or pharmacologically acceptable salts may be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions may also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils.

Under ordinary conditions of storage and use, these preparations generally will contain a preservative to prevent the growth of microorganisms.

Illustrative pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions (for example, see U. S. Patent 5,466,468). In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (*e.g.,* glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and/or vegetable oils. Proper fluidity may be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and/or by the use of surfactants. The prevention of the action of microorganisms can be facilitated by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

In one embodiment, for parenteral administration in an aqueous solution, the solution should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. In this connection, a sterile aqueous medium that can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage may be dissolved in 1 ml of isotonic NaCl solution and either added to 1000 ml of hypodermoclysis fluid or injected at the proposed site of infusion, (see for example, "Remington's Pharmaceutical Sciences" 15th Edition, pages 1035-1038 and 1570-1580). Some variation in dosage will necessarily occur depending on the condition of the subject being treated. Moreover, for human administration, preparations will of course preferably meet sterility, pyrogenicity, and the general safety and purity standards as required by FDA Office of Biologics standards.

In another embodiment of the invention, the compositions disclosed herein may be formulated in a neutral or salt form. Illustrative pharmaceutically-acceptable salts include the acid addition salts (formed with the free

amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like. Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically effective.

The carriers can further comprise any and all solvents, dispersion media, vehicles, coatings, diluents, antibacterial and antifungal agents, isotonic and absorption delaying agents, buffers, carrier solutions, suspensions, colloids, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. The phrase "pharmaceutically-acceptable" refers to molecular entities and compositions that do not produce an allergic or similar untoward reaction when administered to a human.

In certain embodiments, the pharmaceutical compositions may be delivered by intranasal sprays, inhalation, and/or other aerosol delivery vehicles. Methods for delivering genes, nucleic acids, and peptide compositions directly to the lungs *via* nasal aerosol sprays has been described, *e.g.,* in U. S. Patent 5,756,353 and U. S. Patent 5,804,212. Likewise, the delivery of drugs using intranasal microparticle resins (Takenaga *et al.*, J Controlled Release 1998 Mar 2;52(1-2):81-7) and lysophosphatidyl-glycerol compounds (U. S. Patent 5,725,871) are also well-known in the pharmaceutical arts. Likewise, illustrative transmucosal drug delivery in the form of a polytetrafluoroetheylene support matrix is described in U. S. Patent 5,780,045.

In certain embodiments, liposomes, nanocapsules, microparticles, lipid particles, vesicles, and the like, are used for the introduction of the compositions of the present invention into suitable host cells/organisms. In particular, the compositions of the present invention may be formulated for delivery either encapsulated in a lipid particle, a liposome, a vesicle, a nanosphere, or a nanoparticle or the like. Alternatively, compositions of the present invention can be bound, either covalently or non-covalently, to the surface of such carrier vehicles.

The formation and use of liposome and liposome-like preparations as potential drug carriers is generally known to those of skill in the art (see for example, Lasic, Trends Biotechnol 1998 Jul;16(7):307-21; Takakura, Nippon Rinsho 1998

Mar;56(3):691-5; Chandran *et al.*, Indian J Exp Biol. 1997 Aug;35(8):801-9; Margalit, Crit Rev Ther Drug Carrier Syst. 1995;12(2-3):233-61; U.S. Patent 5,567,434; U.S. Patent 5,552,157; U.S. Patent 5,565,213; U.S. Patent 5,738,868 and U.S. Patent 5,795,587, each specifically incorporated herein by reference in its entirety).

Liposomes have been used successfully with a number of cell types that are normally difficult to transfect by other procedures, including T cell suspensions, primary hepatocyte cultures and PC 12 cells (Renneisen *et al.,* J Biol Chem. 1990 Sep 25;265(27):16337-42; Muller *et al.*, DNA Cell Biol. 1990 Apr;9(3):221-9). In addition, liposomes are free of the DNA length constraints that are typical of viral-based delivery systems. Liposomes have been used effectively to introduce genes, various drugs, radiotherapeutic agents, enzymes, viruses, transcription factors, allosteric effectors and the like, into a variety of cultured cell lines and animals. Furthermore, he use of liposomes does not appear to be associated with autoimmune responses or unacceptable toxicity after systemic delivery.

In certain embodiments, liposomes are formed from phospholipids that are dispersed in an aqueous medium and spontaneously form multilamellar concentric bilayer vesicles (also termed multilamellar vesicles (MLVs).

Alternatively, in other embodiments, the invention provides for pharmaceutically-acceptable nanocapsule formulations of the compositions of the present invention. Nanocapsules can generally entrap compounds in a stable and reproducible way (see, for example, Quintanar-Guerrero *et al.*, Drug Dev Ind Pharm. 1998 Dec;24(12):1113-28). To avoid side effects due to intracellular polymeric overloading, such ultrafine particles (sized around 0.1 μm) may be designed using polymers able to be degraded *in vivo*. Such particles can be made as described, for example, by Couvreur *et al.,* Crit Rev Ther Drug Carrier Syst. 1988;5(1):1-20; zur Muhlen *et al.*, Eur J Pharm Biopharm. 1998 Mar;45(2):149-55; Zambaux *et al.* J Controlled Release. 1998 Jan 2;50(1-3):31-40; and U. S. Patent 5,145,684.

Cancer Therapeutic Methods

In further aspects of the present invention, the pharmaceutical compositions described herein may be used for the treatment of cancer, particularly for the immunotherapy of lung cancer. Within such methods, the pharmaceutical compositions described herein are administered to a patient, typically a warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. Pharmaceutical

compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs. As discussed above, administration of the pharmaceutical compositions may be by any suitable method, including administration by intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal, intradermal, anal, vaginal, topical and oral routes.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides as provided herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as $CD8^+$ cytotoxic T lymphocytes and $CD4^+$ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast and/or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known

in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (*see*, for example, Cheever et al., *Immunological Reviews 157*:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated *ex vivo* for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions described herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (*e.g.*, intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (*e.g.*, by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (*i.e.*, untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells *in vitro*. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 25 μg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (*e.g.*, more frequent remissions, complete or partial, or longer disease-free

survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

Cancer Detection and Diagnostic Compositions, Methods and Kits

In general, a cancer may be detected in a patient based on the presence of one or more lung tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, sputum urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as lung cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a lung tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. *See, e.g.*, Harlow and Lane, *Antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the

binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length lung tumor proteins and polypeptide portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μg, and preferably about 100 ng to about 1 μg, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (*see*, *e.g.*, Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody.

Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with lung cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20™. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a

specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as lung cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., *Clinical Epidemiology: A Basic Science for Clinical Medicine*, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (*i.e.*, sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (*i.e.*, the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized

on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1μg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a tumor protein in a biological sample. Within certain methods, a biological sample comprising $CD4^+$ and/or $CD8^+$ T cells isolated from a patient is incubated with a tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated *in vitro* for 2-9 days (typically 4 days) at 37°C with polypeptide (*e.g.*, 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of tumor polypeptide to serve as a control. For $CD4^+$ T cells, activation is preferably detected by evaluating proliferation of the T cells. For $CD8^+$ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*,

hybridizes to) a polynucleotide encoding the tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a tumor protein of the invention that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes hybridize to a polynucleotide encoding a polypeptide described herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence as disclosed herein. Techniques for both PCR based assays and hybridization assays are well known in the art (*see*, for example, Mullis et al., *Cold Spring Harbor Symp. Quant. Biol.*, *51*:263, 1987; Erlich ed., *PCR Technology*, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the compositions described herein may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide(s) evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter

performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

Example 1

Preparation Of Lung Tumor-Specific Cdna Sequences Using Differential Display Rt-Pcr

This example illustrates the preparation of cDNA molecules encoding lung tumor-specific polypeptides using a differential display screen.

Tissue samples were prepared from lung tumor and normal tissue of a patient with lung cancer that was confirmed by pathology after removal of samples from the patient. Normal RNA and tumor RNA was extracted from the samples and mRNA was isolated and converted into cDNA using a $(dT)_{12}AG$ (SEQ ID NO: 47) anchored 3' primer. Differential display PCR was then executed using a randomly chosen primer (SEQ ID NO: 48). Amplification conditions were standard buffer containing 1.5 mM $MgCl_2$, 20 pmol of primer, 500 pmol dNTP and 1 unit of Taq DNA polymerase (Perkin-Elmer, Branchburg, NJ). Forty cycles of amplification were performed using 94 °C denaturation for 30 seconds, 42 °C annealing for 1 minute and 72 °C extension for 30 seconds. Bands that were repeatedly observed to be specific to the RNA fingerprint pattern of the tumor were cut out of a silver stained gel, subcloned into the pGEM-T vector (Promega, Madison, WI) and sequenced. The isolated 3' sequences are provided in SEQ ID NO: 1-16.

Comparison of these sequences to those in the public databases using the BLASTN program, revealed no significant homologies to the sequences provided in SEQ ID NOs:1-11. To the best of the inventors' knowledge, none of the isolated DNA sequences have previously been shown to be expressed at a greater level in human lung tumor tissue than in normal lung tissue.

Example 2

Use of Patient Sera to Identify dna Sequences Encoding Lung tumor antigens

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by expression screening of lung tumor samples with autologous patient sera.

A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human squamous epithelial lung carcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). The resulting library was

screened using *E. coli*-absorbed autologous patient serum, as described in Sambrook et al., (*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989), with the secondary antibody being goat anti-human IgG-A-M (H + L) conjugated with alkaline phosphatase, developed with NBT/BCIP (Gibco BRL). Positive plaques expressing immunoreactive antigens were purified. Phagemid from the plaques was rescued and the nucleotide sequences of the clones was determined.

Fifteen clones were isolated, referred to hereinafter as LT86-1 – LT86-15. The isolated cDNA sequences for LT86-1 – LT86-8 and LT86-10 - LT86-15 are provided in SEQ ID NO:17-24 and 26-31, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NOs:32-39 and 41-46, respectively. The determined cDNA sequence for LT86-9 is provided in SEQ ID NO:25, with the corresponding predicted amino acid sequences from the 3' and 5' ends being provided in SEQ ID NOs:40 and 65, respectively. These sequences were compared to those in the gene bank as described above. Clones LT86-3, LT86-6 – LT86-9, LT86-11 – LT86-13 and LT86-15 (SEQ ID NO: 19, 22-25, 27-29 and 31, respectively) were found to show some homology to previously identified expressed sequence tags (ESTs), with clones LT86-6, LT86-8, LT86-11, LT86-12 and LT86-15 appearing to be similar or identical to each other. Clone LT86-3 was found to show some homology with a human transcription repressor. Clones LT86-6, 8, 9, 11, 12 and 15 were found to show some homology to a yeast RNA Pol II transcription regulation mediator. Clone LT86-13 was found to show some homology with a *C. elegans* leucine aminopeptidase. Clone LT86-9 appears to contain two inserts, with the 5' sequence showing homology to the previously identified antisense sequence of interferon alpha-induced P27, and the 3' sequence being similar to LT86-6. Clone LT86-14 (SEQ ID NO:30) was found to show some homology to the trithorax gene and has an "RGD" cell attachment sequence and a beta-Lactamase A site which functions in hydrolysis of penicillin. Clones LT86-1, LT86-2, LT86-4, LT86-5 and LT86-10 (SEQ ID NOs:17, 18, 20, 21 and 26, respectively) were found to show homology to previously identified genes. A subsequently determined extended cDNA sequence for LT86-4 is provided in SEQ ID NO:66, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 67.

Subsequent studies led to the isolation of five additional clones, referred to as LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27. The determined 5' cDNA sequences for LT86-20, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 68 and 70-72, respectively, with the determined 3' cDNA sequences for LT86-21 being

provided in SEQ ID NO: 69. The corresponding predicted amino acid sequences for LT86-20, LT86-21, LT86-22, LT86-26 and LT86-27 are provided in SEQ ID NO: 73-77, respectively. LT86-22 and LT86-27 were found to be highly similar to each other. Comparison of these sequences to those in the gene bank as described above, revealed no significant homologies to LT86-22 and LT86-27. LT86-20, LT86-21 and LT86-26 were found to show homology to previously identified genes.

In further studies, a cDNA expression library was prepared using mRNA from a lung small cell carcinoma cell line in the lambda ZAP Express expression vector (Stratagene), and screened as described above, with a pool of two lung small cell carcinoma patient sera. The sera pool was adsorbed with *E. coli* lysate and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue. Seventy-three clones were isolated. The determined cDNA sequences of these clones are provided in SEQ ID NO: 290-362. The sequences of SEQ ID NO: 289-292, 294, 296-297, 300, 302, 303, 305, 307-315, 317-320, 322-325, 327-332, 334, 335, 338-341, 343-352, 354-358, 360 and 362 were found to show some homology to previously isolated genes. The sequences of SEQ ID NO: 293, 295, 298, 299, 301, 304, 306, 316, 321, 326, 333, 336, 337, 342, 353, 359 and 361 were found to show some homology to previously identified ESTs.

Example 3

Use of Mouse Antisera to Identify DNA Sequences Encoding Lung Tumor Antigens

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared as described above in Example 2. Sera was obtained from SCID mice containing late passaged human squamous cell and adenocarcinoma tumors. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 200,000 PFUs were screened from the unamplified library using this antiserum. Using a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (BRL Labs.), approximately 40 positive plaques were identified. Phage was purified and phagemid excised for 9 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 7 of the isolated clones (hereinafter referred to as L86S-3, L86S-12, L86S-16, L86S-25, L86S-36, L86S-40 and L86S-46) are provided in SEQ ID NO: 49-55, with the corresponding predicted amino acid

sequences being provided in SEQ ID NO: 56-62, respectively. The 5' cDNA sequences for the remaining 2 clones (hereinafter referred to as L86S-30 and L86S-41) are provided in SEQ ID NO: 63 and 64. L86S-36 and L86S-46 were subsequently determined to represent the same gene. Comparison of these sequences with those in the public database as described above, revealed no significant homologies to clones L86S-30, L86S-36 and L86S-46 (SEQ ID NO: 63, 53 and 55, respectively). L86S-16 (SEQ ID NO: 51) was found to show some homology to an EST previously identified in fetal lung and germ cell tumor. The remaining clones were found to show at least some degree of homology to previously identified human genes. Subsequently determined extended cDNA sequences for L86S-12, L86S-36 and L86S-46 are provided in SEQ ID NO: 78-80, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 81-83.

Subsequent studies led to the determination of 5' cDNA sequences for an additional nine clones, referred to as L86S-6, L86S-11, L86S-14, L86S-29, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 (SEQ ID NO: 84-92, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NO: 93-101, respectively. L86S-30, L86S-39 and L86S-47 were found to be similar to each other. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to L86S-14. L86S-29 was found to show some homology to a previously identified EST. L86S-6, L86S-11, L86S-34, L86S-39, L86S-47, L86S-49 and L86S-51 were found to show some homology to previously identified genes.

In further studies, a directional cDNA library was constructed using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was isolated from two primary squamous lung tumors and poly A+ RNA was isolated using an oligo dT column. Antiserum was developed in normal mice using a pool of sera from three SCID mice implanted with human squamous lung carcinomas. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli* absorbed mouse anti-SCID tumor serum. Positive plaques were identified as described above. Phage was purified and phagemid excised for 180 clones with inserts in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined cDNA sequences for 23 of the isolated clones are provided in SEQ ID NO: 126-148. Comparison of these sequences with those in the public database as described above revealed no significant homologies to the sequences of SEQ ID NO: 139 and 143-148. The sequences of SEQ ID NO: 126-138 and 140-142

were found to show homology to previously identified human polynucleotide sequences.

Example 4

USE OF MOUSE ANTISERA TO SCREEN LUNG TUMOR LIBRARIES PREPARED FROM SCID MICE

This example illustrates the isolation of cDNA sequences encoding lung tumor antigens by screening of lung tumor cDNA libraries prepared from SCID mice with mouse anti-tumor sera.

A directional cDNA lung tumor expression library was prepared using a Stratagene kit with a Lambda Zap Express vector. Total RNA for the library was taken from a late passaged lung adenocarcinoma grown in SCID mice. Poly A+ RNA was isolated using a Message Maker Kit (Gibco BRL). Sera was obtained from two SCID mice implanted with lung adenocarcinomas. These sera were pooled and injected into normal mice to produce anti-lung tumor serum. Approximately 700,000 PFUs were screened from the unamplified library with *E. coli*-absorbed mouse anti-SCID tumor serum. Positive plaques were identified with a goat anti-mouse IgG-A-M (H+L) alkaline phosphatase second antibody developed with NBT/BCIP (Gibco BRL). Phage was purified and phagemid excised for 100 clones with insert in a pBK-CMV vector for expression in prokaryotic or eukaryotic cells.

The determined 5' cDNA sequences for 33 of the isolated clones are provided in SEQ ID NO: 149-181. The corresponding predicted amino acid sequences for SEQ ID NO: 149, 150, 152-154, 156-158 and 160-181 are provided in SEQ ID NO: 182, 183, 186, 188-193 and 194-215, respectively. The clone of SEQ ID NO: 151 (referred to as SAL-25) was found to contain two open reading frames (ORFs). The predicted amino acid sequences encoded by these ORFs are provided in SEQ ID NO: 184 and 185. The clone of SEQ ID NO: 153 (referred to as SAL-50) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 187 and 216. Similarly, the clone of SEQ ID NO: 155 (referred to as SAL-66) was found to contain two open reading frames encoding the predicted amino acid sequences of SEQ ID NO: 189 and 190. Comparison of the isolated sequences with those in the public database revealed no significant homologies to the sequences of SEQ ID NO: 151, 153 and 154. The sequences of SEQ ID NO: 149, 152, 156, 157 and 158 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 150, 155 and 159-181 were found to show homology to sequences previously identified in humans.

Using the procedures described above, two directional cDNA libraries (referred to as LT46-90 and LT86-21) were prepared from two late passaged lung squamous carcinomas grown in SCID mice and screened with sera obtained from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 217-237 and 286-289. SEQ ID NO: 286 was found to be a longer sequence of LT4690-71 (SEQ ID NO: 237). Comparison of these sequences with those in the public databases revealed no known homologies to the sequences of SEQ ID NO: 219, 220, 225, 226, 287 and 288. The sequences of SEQ ID NO: 218, 221, 222 and 224 were found to show some homology to previously identified sequences of unknown function. The sequence of SEQ ID NO: 236 was found to show homology to a known mouse mRNA sequence. The sequences of SEQ ID NO: 217, 223, 227-237, 286 and 289 showed some homology to known human DNA and/or RNA sequences.

In further studies using the techniques described above, one of the cDNA libraries described above (LT86-21) was screened with *E. coli*-absorbed mouse anti-SCID tumor serum. This serum was obtained from normal mice immunized with a pool of 3 sera taken from SCID mice implanted with human squamous lung carcinomas. The determined cDNA sequences for the isolated clones are provided in SEQ ID NO: 238-285. Comparison of these sequences with those in the public databases revealed no significant homologies to the sequences of SEQ ID NO: 253, 260, 277 and 285. The sequences of SEQ ID NO: 249, 250, 256, 266, 276 and 282 were found to show some homology to previously isolated expressed sequence tags (ESTs). The sequences of SEQ ID NO: 238-248, 251, 252, 254, 255, 257-259, 261-263, 265, 267-275, 278-281, 283 and 284 were found to show some homology to previously identified DNA or RNA sequences.

The expression levels of certain of the isolated antigens in lung tumor tissues compared to expression levels in normal tissues was determined by microarray technology. The results of these studies are shown below in Table 2, together with the databank analyses for these sequences.

TABLE 2

Clone	SEQ ID NO:	Description	LT+ F/N	SCC+M/ N	Squa/ N	Adeno/ N
2LT-3	238	Unknown (KIAA0712)	2.2	3.8	3.3	-
2LT-6	239	Lactate DH B	2.3	3.8	4.1	-
2LT-22	240	Fumarate hydratase	-	3.0	-	-
2LT-26	242	CG1-39	-	-	12.8	-
2LT-31	243	ADH7	-	-	8.4	2.2
2LT-36	244	ADH7	-	2.4	2.0	-
2LT-42	245	HMG-CoA synthase	2.2	2.6	2.2	-
2LT-54	247	(Mus) ninein	-	2.1	-	-
2LT-55	248	Ubiquitin	2.2	-	2.5	2.0
2LT-57	249	Novel	2.1	2.9	2.4	-
2LT-58	250	Novel	2.3	4.0	2.9	-
2LT-59	251	Unknown KIAA0784	2.4	3.0	2.3	2.0
2LT_62	252	Nuc Pore Cmplx-ass pro TPR	-	-	-	2.1
2LT-70	256	Unknown KIAA0871	-	2.5	2.2	2.1
2LT-73	257	Mus polyadenylate-binding	-	2.0	-	-
2LT-76	259	Trans-Golgi p230	2.1	-	2.6	-
2LT-85	263	Ribosomal protein (LS29)	-	-	-	2.1
2LT-89	265	Unknown PAC212G6	-	2.0	-	-
2LT-98	268	Melanoma diff assoc pro 9	-	-	-	2.2
2LT-100	269	Mus Collagen alpha VI	-	-	-	2.1
2LT-105	271	NY-CO-7 antigen	-	3.2	-	-
2LT-108	273	Unknown RG363M04	-	3.1	-	-
2LT-124	279	Galectin-9 (secreted)	2.3	2.7	2.0	-
2LT-126	280	L1 element L1.33 p40	2.5	-	3.1	-
2LT-128	282	Novel (kappa B-ras 2)	2.3+	-	20.4	2.5
2LT-133	284	Alpha II spectrin	-	2.3	-	-

LT+F/N = Lung Tumor plus Fetal tissue over Normal tissues

SC+M/N = Lung Small Cell carcinoma plus Metastatic over Normal tissues

Squa/N = Squamous lung tumor over Normal tissues

Aden/N = Adenocarcinoma over Normal tissues

Full-length sequencing studies on antigen 2LT-128 (SEQ ID NO: 282) resulted in the isolation of the full-length cDNA sequence provided in SEQ ID NO: 392. This amino acid sequence encoded by this full-length cDNA sequence is provided in SEQ ID NO: 393. This antigen shows 20-fold over-expression in squamous cell carcinoma and 2.5-fold over-expression in lung adenocarcinoma. This gene has been described as a potential ras oncogene (Fenwick et al. *Science, 287*:869-873, 2000).

Extended sequence information was obtained for clones 2LT-3 (SEQ ID NO:238), 2LT-26 (SEQ ID NO:242), 2LT-57 (SEQ ID NO: 249), 2LT-58 (SEQ ID NO:250), 2LT-98 (SEQ ID NO:268) and 2LT-124 (SEQ ID NO:279). The extended cDNA sequences for these clones are set forth in SEQ ID NOs:428-433, respectively, encoding the polypeptide sequences set forth in SEQ ID NOs: 434-439, respectively.

Example 5

Determination Of Tissue Specificity Of Lung Tumor Polypeptides

Using gene specific primers, mRNA expression levels for representative lung tumor polypeptides were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent. First strand synthesis was carried out using 2 μg of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42 ^{0}C for one hour. The cDNA was then amplified by PCR with gene-specific primers. To ensure the semi-quantitative nature of the RT-PCR, β-actin was used as an internal control for each of the tissues examined. 1 μl of 1:30 dilution of cDNA was employed to enable the linear range amplification of the β-actin template and was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the β-actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in five different types of tumor tissue (lung squamous tumor from 3 patients, lung adenocarcinoma, prostate tumor, colon tumor and lung tumor), and different normal tissues, including lung from four

patients, prostate, brain, kidney, liver, ovary, skeletal muscle, skin, small intestine, myocardium, retina and testes. L86S-46 was found to be expressed at high levels in lung squamous tumor, colon tumor and prostate tumor, and was undetectable in the other tissues examined. L86S-5 was found to be expressed in the lung tumor samples and in 2 out of 4 normal lung samples, but not in the other normal or tumor tissues tested. L86S-16 was found to be expressed in all tissues except normal liver and normal stomach. Using real-time PCR, L86S-46 was found to be over-expressed in lung squamous tissue and normal tonsil, with expression being low or undetectable in all other tissues examined.

Example 6

ISOLATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS

DNA sequences encoding antigens potentially involved in squamous cell lung tumor formation were isolated as follows.

A lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a pool of two human squamous epithelial lung carcinomas and poly A+ RNA was isolated using oligo-dT cellulose (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined cDNA sequence for the clone SLT-T1 is provided in SEQ ID NO: 102, with the determined 5' cDNA sequences for the clones SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9, SLT-T10, SLT-T11 and SLT-T12 being provided in SEQ ID NO: 103-110, respectively. The corresponding predicted amino acid sequence for SLT-T1, SLT-T2, SLT-T3, SLT-T10 and SLT-T12 are provided in SEQ ID NO: 111-115, respectively. Comparison of the sequences for SLT-T2, SLT-T3, SLT-T5, SLT-T7, SLT-T9 and SLT-T11 with those in the public databases as described above, revealed no significant homologies. The sequences for SLT-T10 and SLT-T12 were found to show some homology to sequences previously identified in humans.

The sequence of SLT-T1 was determined to show some homology to a PAC clone of unknown protein function. The cDNA sequence of SLT-T1 (SEQ ID NO: 102) was found to contain a mutator (MUTT) domain. Such domains are known to function in removal of damaged guanine from DNA that can cause A to G transversions (see, for example, el-Deiry, W.S., 1997 *Curr. Opin. Oncol. 9*:79-87; Okamoto, K. et al. 1996 *Int. J. Cancer 65*:437-41; Wu, C. et al. 1995 *Biochem. Biophys. Res. Commun. 214*:1239-45; Porter, D.W. et al. 1996 *Chem. Res. Toxicol. 9*:1375-81). SLT-T1 may

thus be of use in the treatment, by gene therapy, of lung cancers caused by, or associated with, a disruption in DNA repair.

In further studies, DNA sequences encoding antigens potentially involved in adenocarcinoma lung tumor formation were isolated as follows. A human lung tumor directional cDNA expression library was constructed employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Total RNA for the library was taken from a late SCID mouse passaged human adenocarcinoma and poly A+ RNA was isolated using the Message Maker kit (Gibco BRL, Gaithersburg, MD). Phagemid were rescued at random and the cDNA sequences of isolated clones were determined.

The determined 5' cDNA sequences for five isolated clones (referred to as SALT-T3, SALT-T4, SALT-T7, SALT-T8, and SALT-T9) are provided in SEQ ID NO: 116-120, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 121-125. SALT-T3 was found to show 98% identity to the previously identified human transducin-like enhancer protein TLE2. SALT-T4 appears to be the human homologue of the mouse H beta 58 gene. SALT-T7 was found to have 97% identity to human 3-mercaptopyruvate sulfurtransferase and SALT-T8 was found to show homology to human interferon-inducible protein 1-8U. SALT-T9 shows approximately 90% identity to human mucin MUC 5B.

cDNA sequences encoding antigens potentially involved in small cell lung carcinoma development were isolated as follows. cDNA expression libraries were constructed with mRNA from the small cell lung carcinoma cell lines NCIH69, NCIH128 and DMS79 (all available from the American Type Culture Collection, Manassas, VA) employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Phagemid were rescued at random and the cDNA sequences of 27 isolated clones were determined. Comparison of the determined cDNA sequences revealed no significant homologies to the sequences of SEQ ID NO: 372 and 373. The sequences of SEQ ID NO: 364, 369, 377, 379 and 386 showed some homology to previously isolated ESTs. The sequences of the remaining 20 clones showed some homology to previously identified genes. The cDNA sequences of these clones are provided in SEQ ID NO: 363, 365-368, 370, 371, 374-376, 378, 380-385 and 387-389, wherein SEQ ID NO: 363, 366-368, 370, 375, 376, 378, 380-382, 384 and 385 are full-length sequences.

Comparison of the cDNA sequence of SEQ ID NO: 372 indicated that this clone (referred to as 128T1) is a novel member of a family of putative seven pass transmembrane proteins. Specifically, using the computer algorithm PSORT, the protein was predicted to be a type IIIA plasma membrane seven pass transmembrane protein. A genomic clone was identified in the Genbank database which contained the

predicted N-terminal 58 amino acids missing from the amino acid sequence encoded by SEQ ID NO: 372. The determined full-length cDNA sequence for the 128T1 clone is provided in SEQ ID NO: 390, with the corresponding amino acid sequence being provided in SEQ ID NO: 391.

The expression levels of certain of the isolated antigens in lung tumor tissues compared to expression levels in normal tissues was determined by microarray technology. The results of these studies are shown below in Table 3, together with the databank analyses for these sequences.

TABLE 3

Clone	SEQ ID NO:	Description	LT+ F/N	SCC+ M/N	Squa/N	Adeno/ N
DMS79-T1	363	STAT-ind inhib of cytokine	-	2.0	-	-
DMS79-T6	367	Neuronal cell death related	-	2.2	-	-
DMS79-T9	369	Novel	-	2.2	-	-
DMS79-T10	370	Ubiquitin carrier protein	-	3.9	2.2	-
DMS79-T11	371	HPV16E1 pro binding protein	-	2.1	-	-
128-T9	378	Elongation factor 1 alpha	-	2.7	-	-
128T11	380	Malate dehyrogenase	-	2.3	2.0	-
128-T12	381	Apurinic/apyrim endonuclease	-	5.4	-	-
NCIH69-T3	382	Sm-like protein CaSm	-	-	2.4	-
NCIH69-T6	384	Transcription factor BTF3a	-	2.5	-	-

LT+F/N = Lung Tumor plus Fetal tissue over Normal tissues

SC+M/N = Lung Small Cell carcinoma plus Metastatic over Normal tissues

Squa/N = Squamous lung tumor over Normal tissues

Aden/N = Adenocarcinoma over Normal tissues

Example 7

SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

Example 8

ISOLATION AND CHARACTERIZATION OF DNA SEQUENCES ENCODING LUNG TUMOR ANTIGENS BY T-CELL EXPRESSION CLONING

Lung tumor antigens may also be identified by T cell expression cloning. One source of tumor specific T cells is from surgically excised tumors from human patients.

A non-small cell lung carcinoma was minced and enzymatically digested for several hours to release tumor cells and infiltrating lymphocytes (tumor infiltrating T cells, or TILs). The cells were washed in HBSS buffer and passed over a Ficoll (100%/75%/HBSS) discontinuous gradient to separate tumor cells and lymphocytes from non-viable cells. Two bands were harvested from the interfaces; the upper band at the 75%/HBSS interface contained predominantly tumor cells, while the lower band at the 100%/75%/HBSS interface contained a majority of lymphocytes. The TILs were expanded in culture, either in 24-well plates with culture media supplemented with 10 ng/ml IL-7 and 100 U/ml IL-2, or alternatively, 24-well plates that have been pre-coated with the anti-CD3 monoclonal antibody OKT3. The resulting TIL cultures were analyzed by FACS to confirm that a high percentage were CD8+ T cells (>90% of gated population) with only a small percentage of CD4+ cells.

In addition, non-small cell lung carcinoma cells were expanded in culture using standard techniques to establish a tumor cell line (referred to as LT391-06), which was later confirmed to be a lung carcinoma cell line by immunohistochemical analysis. This tumor cell line was transduced with a retroviral vector to express human CD80, and characterized by FACS analysis to confirm high expression levels of CD80, class I MHC and class II MHC molecules.

The ability of the TIL lines to specifically recognize autologous lung tumor was demonstrated by cytokine release assays (IFN-γ and TNF-α) as well as ^{51}Cr release assays. Briefly, TIL cells from day 21 cultures were co-cultured with either autologous or allogeneic tumor cells, EBV-immortalized LCL, or control cell lines Daudi and K562, and the culture supernatant monitored by ELISA for the presence of cytokines. The TIL specifically recognized autologous tumor but not allogeneic tumor. In addition, there was no recognition of EBV-immortalized LCL or the control cell lines, indicating that the TIL lines are tumor specific and are potentially recognizing a tumor antigen presented by autologous MHC molecules.

The characterized tumor-specific TIL lines were expanded to suitable numbers for T cell expression cloning using soluble anti-CD3 antibody in culture with irradiated EBV transformed LCLs and PBL feeder cells in the presence of 20 U/ml IL-2. Clones from the expanded TIL lines were generated by standard limiting dilution techniques. Specifically, TIL cells were seeded at 0.5 cells/well in a 96-well U bottom plate and stimulated with CD-80-transduced autologous tumor cells, EBV transformed LCL, and PBL feeder cells in the presence of 50 U/ml IL-2. The specificity of these clones for autologous tumor was confirmed by ^{51}Cr microcytotoxicity and IFN-γ bioassays.

These CTL clones were demonstrated to be HLA-B/C restricted by antibody blocking experiments. A representative CTL clone was tested on a panel of allogeneic lung carcinomas and it recognized both autologous tumor and a lung squamous cell carcinoma (936T). As the only class I MHC molecule shared among these tumors was HLA-Cw1203, this indicated that this was the restriction element used by the CTL. This finding was confirmed by the recognition of a number of allogeneic lung carcinomas transduced with a retroviral vector encoding HLA-Cw1203 by the CTL.

PolyA mRNA was prepared from a lung tumor cell line referred to as LT391-06 using Message Maker (Life Technologies; Rockville, MD). The subsequent steps involving cDNA synthesis were performed according to Life Technologies cloning manual (SuperScript Plasmid System for cDNA Synthesis and Plasmid

Cloning). Modifications to the protocol were made as follows. At the adapter addition step, EcoRI-XmnI adapters (New England Biolabs; Beverly, MA) were substituted. Size fractionated cDNAs were ligated into the expression vector system HisMax A, B, C (Invitrogen; Carlsbad, CA) to optimize for protein expression in all three coding frames. Library plasmids were then aliquotted at approximately 100 CFU/well into a 96-well block for overnight liquid amplification. From these cultures, glycerol stocks were made and pooled plasmid was prepared by automated robot (Qiagen; Valencia, CA). The concentration of the plasmid DNA in each well of the library plates was determined to be approximately 150 ng/ul. Initial characterization of the cDNA expression library was performed by randomly sequencing 24 primary transformants and subjecting the resulting sequences to BLAST searches against available databases. The determined cDNA sequences are provided in SEQ ID NO: 443-480, with the results of the BLAST searches being provided in Table 4.

TABLE 4

Clone	SEQ ID NO:	GenBank Accession	Description
55163	458, 459		*Novel in Genbank*
55158	452		*Novel in Genbank*
Homology to known sequences with unknown function			
55153	443, 444	7018516	H. sapiens mRNA; cDNA DKFZp434M035
55154	445, 446	6437562	H. sapiens Chr 22q11 PAC Clone p393
55157	450, 451	2887408	H. sapiens KIAA0417 mRNA
55165	462, 463	3970871	H. sapiens HRIHFB2122 mRNA
Homology to known sequences with known function			
55155	447	7677405	H. sapiens F-box protein FBS (FBS)
55156	448, 449	3929584	H. sapiens EEN pseudogene
55161	454, 455	4503350	H. sapiens DNA (cytosine-5-)-methyltransferase 1 (DNMT1)
55162	456, 457	31220	ERK1 mRNA for protein serine/threonine kinase
55164	460, 461	6677666	H. sapiens RNA-binding protein (autoantigenic) (RALY)
55166	464, 465	3249540	H. sapiens ribonuclease P protein subunit p40 (RPP40)
55167	466, 467	7657497	H. sapiens renal tumor antigen (RAGE)
55168	468, 469	2873376	H. sapiens exportin t mRNA
55169	470, 471	3135472	H. sapiens Cre binding protein-like 2

Clone	SEQ ID NO:	GenBank Accession	Description
			mRNA
55171	474	4759151	H. sapiens spermine synthase (SMS)
55173	476	6688148	H. sapiens partial mRNA for NICE-3 protein
55174	477, 478	531394	Human transcriptional coactivator PC4
55175	479	6563201	H. sapiens translation initiation factor eIF-2b delta subunit
55176	480	29860	hCENP-Bgene, for centromere autoantigen B (CENP-B)
Homology to Ribosomal Protein			
55159	453	337494	Ribosomal protein L7a (surf 3) large subunit mRNA
55170	472, 473	4506648	H.sapiens mRNA for ribosomal protein L3
55172	475	388031	H. sapiens ribosomal protein L11

For T cell screening, approximately 80 ng of the library plasmid DNA and 80 ng of HLA-Cw1203 plasmid DNA was mixed with the lipid Fugene according to the manufacturers' instructions and transfected in duplicate into COS-7 cells. After incubation at 37 °C for 48 hours, the transfection mixture was removed and 10,000 LT391-06 CTL were added to each well in fresh media containing human serum.

The ability of T cells to recognize an antigen in the library was assessed by cytokine release after 6 hours (TNF-alpha, WEHI bio-assay) or after 24 hours (IFN-gamma, ELISA). Approximately 2.0 x 10^5 clones (in plasmid pools of 100) were screened using this system in COS-7 cells. Three plasmid pools were identified (referred to as 14F10, 19A4, and 20E10) that were recognized by LT391-06 CTL. Transfection of these plasmid pools into COS-7 cells led to production of both IFN-gamma and TNF-alpha from the LT391-06 CTL at levels significantly above background. Pools 14F10, 19A4 and 20E10 were "broken down" into several hundred individual plasmid DNAs and retested. The sequences of 24 novel clones isolated from pool 14F10 are provided in SEQ ID NO: 481-511.

One plasmid (3D9) from pool 14F10, one plasmid from pool 20E10 and 5 plasmids (2A6, 2E11, 2F12, 3F4, 3H8) from pool 19A4 were capable of reconstituting T cell recognition. Sequencing of these plasmids led to the identification of a 7.8 kB cDNA insert (referred to as clone 14F10), a 2.2 kB cDNA insert (referred to as clone 19A4; SEQ ID NO:440), and a clone referred to as 20E10. The full-length cDNA sequence for 14F10 is provided in SEQ ID NO: 441. Clone 14F10 does not contain the first two "G" nucleotides found at the 5' end of 19A4, and the 3'-proximal

24 bp of 19A4 differ from the corresponding region of 14F10 (nucleotides 2145-2165). Furthermore, 3837 bp of 3' additional sequence was isolated for clone 14F10. The 5' terminal cDNA sequence (337 bp) of clone 20E10 is provided in SEQ ID NO: 442. 20E10 contains an additional 3 nucleotides (as compared to 19A4) at the 5'-most end. The additional sequence from the 5' end of clone 20E10 contains an "ATG" and therefore appears to contain the translational start site of a novel open reading frame. BLAST search analysis against the GenBank database identified these sequences as having significant homology with a truncated human cystine/glutamate transporter gene. Unlike the published sequence, however, clones 14F10 and 19A4 contain a unique 5' terminus consisting of 181 nucleotides. This novel sequence replaces the published 5' region and results in the removal of the reported initiating methionine (start codon) and an additional two amino acids of the reported transporter protein. Therefore, the translated product of clones 14F10 and 19A4 is different than the cystine/glutamate transporter protein. Furthermore, T cell recognition of other lung tumors demonstrates that this antigen is expressed by other tumors as well.

The epitope and amino acid sequence encoded within clones 19A4 and 14F10 which reconstitutes T cell recognition of anti-LT391-06 cells were mapped as follows. Cos-7 cells were transfected with 80 ng/well HLA-Cw1203 along with titrated amounts of cDNA encoding clone 19A4, a potential open reading frame located in the unique 5' terminus of 19A4, or the open reading frame from the cystine/glutamate (Cys-Glu) transporter gene, cloned into a eukaryotic expression vector and tested for stimulation of anti-LT391-06 T cells in a TNF assay. As a positive control Cos-7 cells were co-transfected with HLA-Cw1203 and the positive plasmid clone 19A4 described above. The Cys-Glu transporter expression construct was isolated by PCR using 5' and 3' primers specific for the known ORF of the transporter with 19A4 as template. In addition, each 5' primer contained a Kozak translation initiation site and starting methionine to drive translation of the polypeptide. CTL against LT391-06 did not recognize transfectants expressing the Cys-Glu transporter construct, but did recognize transfectants expressing 19A4 and the 5' ORF from 19A4.

In subsequent experiments, Cos-7 cells were co-transfected with 80 ng/well HLA-Cw1203 along with titrated amounts of DNA of transposition mutants F10 and C12, respectively, and tested for simulation of anti-LT391-06 T cells in a TNF assay. As a positive control, Cos-7 cells were co-transfected with HLA-Cw1203 and clones of the 5' ORF of 19A4. Transposition mutants F10 and C12 were obtained by transposon-mediated mutation of the 14F10 clone and screening for insertion site by sequence analyses. The transposon of mutant F10 is inserted approximately 304 bp

from the 5' EcoRI cloning site of the 14F10 cDNA. This mutation did not disrupt translation of the T cell epitope. By contrast, the transposon of mutant C12, which is inserted approximately 116 bp from the 5' EcoRI cloning site of the 14F10 cDNA, was found to interrupt translation of the T cell eptiope. Thus the epitope in 14F10 maps between these two transposon insertion sites. The amino acid sequence of the region between the C12 and F10 transposon insertion sites is provided in SEQ ID NO: 586.

A series of 11 overlapping 16-mer and 15-mer peptides for the region shown in SEQ ID NO: 586 were prepared and tested for stimulation of anti-LT391-06 cells, as determined by cytokine release in TNF and IFN-γ assays. Only the peptide provided in SEQ ID NO: 587 (corresponding to residues 5-20 of SEQ ID NO: 586) stimulated cytokine release. These studies demonstrate that the HLA-Cw1203 restricted epitope of the LT391-06 antigen is contained within SEQ ID NO: 587.

Example 9

Isolation and Characterization of DNA Sequences Encoding Lung Tumor Antigens by PCR Subtraction

This example describes the isolation and characterization of cDNA clones from a PCR subtracted expression library prepared from the human lung tumor cell line LT391-06 described above.

Tester poly A mRNA was prepared from the cell line LT391-06 as described above. Driver poly A mRNA was isolated from a human acute T cell leukemia/T lymphocyte cell line (Jurkat) which is derived from non-lung cells and is not recognized by LT391-06 reactive T cells. The subtraction was performed according to the method of Clontech (Palo Alto, CA) with the following changes: 1) a second restriction digestion reaction of cDNA was completed using a pool of enzymes (MscI, PvuII, StuI and DraI). This was in addition to, and separate from, the Clontech recommended single restriction enzyme digestion with RsaI. Each restriction digest set was treated as a separate library to ensure that the final mixed library contained overlapping fragments. Thus, the epitope recognized by the T cells should be represented on a fragment within the library and not destroyed by the presence of a single restriction site within it. 2) The ratio of driver to tester cDNA was increased in the hybridization steps to increase subtraction stringency. To analyze the efficiency of the subtraction, actin was PCR amplified from dilutions of subtracted, as well as unsubtracted, PCR samples. The second amplification step utilized primers that were modified from those normally used. Three nested PCR primers were engineered to contain a cleavable EcoRI site (not utilized during cloning) that was in one of three

frames. Thus, secondary amplification with these primers resulted in products that could be ligated directly into the eukaryotic expression plasmid pcDNA4His/Max-Topo (Invitrogen). This resulted in the PCR subtracted and amplified fragments being represented in-frame somewhere within the library. Due to the mechanics of the subtraction only 50% of fragments will be in the correct orientation. The complexity and redundancy of the library was characterized by sequencing 96 randomly picked clones from the final pooled PCR subtraction expression library, referred to as LT391-06PCR. These sequences (SEQ ID NO: 512-581) were analyzed by comparison to sequences in publicly available databases (Table 5).

TABLE 5

Clone	SEQ ID NO:	GenBank Accession	Description
57235	532		*Novel in Genbank*
57255	547		*Novel in Genbank*
57264	554		*Novel in Genbank*
Homology to known sequences with unknown function			
57215	518	5689540	H. sapiens mRNA for KIAA1102 protein
57223	522	2341006	Human Xq13 3' end of PAC 92E23
57227	524	7022540	H. sapiens cDNA FLJ10480 fis, clone NT2RP2000126
57238	535	6807795	H. sapiens mRNA; cDNA DKFZp761G02121
57239	536	5757546	H. sapiens clone DJ0823F17
57243	539	7023805	H. sapiens cDNA FLJ11259 fis, clone PLACE1009045
57245	540	4884472	H. sapiens mRNA; cDNA DKFZp586O2223
57267	557	6808218	H. sapiens mRNA; cDNA DKFZp434O1519
57268	558	10040400	Sequence 12 from Patent WO9954460
57270	560	7959775	H. sapiens PRO1489 mRNA
57271	561	4500158	H. sapiens mRNA; cDNA DKFZp586B0918
57281	567	6560920	H. sapiens clone RP11- 501O7
57283	569	285962	Human mRNA for KIAA0108 gene
57285	570	7019813	H. sapiens cDNA FLJ20002 fis, clone ADKA01577
Homology to known sequences with known function			
57207	512	517176	H. sapiens YAP65 mRNA

Clone	SEQ ID NO:	GenBank Accession	Description
57210	514	6841233	H. sapiens HSPC292 mRNA
57211	515	2606093	H. sapiens Cyr61 protein (CYR61) mRNA
57212	516	339648	Human thioredoxin (TXN) mRNA
57219	519	4504616	H. sapiens insulin- like growth factor binding protein 3 (IGFBP3)
57221	520	7274241	H. sapiens novel retinal pigment epithelial cell protein (NORPEG)
57222	521	189564	Human, plasminogen activator inhibitor- 1 gene
57228	525	4757755	H. sapiens annexin A2 (ANXA2)
57230	527	180800	Human alpha- 1 collagen type IV gene, exon 52
57232	529	6729061	H. sapiens clone RPC11- 98D12 from 7q31
57233	530	338391	Spermidine/ spermine N1- acetyltransferase
57234	531	7305302	H. sapiens NCK- associated protein 1 (NCKAP1)
57236	533	4929722	H. sapiens CGI- 127 protein
57242	538	4503558	H. sapiens epithelial membrane protein 1 (EMP1)
57248	541	183585	Human pregnancy- specific beta- glycoprotein c
57250	543	4759283	H. sapiens ubiquitin carboxyl- terminal esterase L1 (UCHL1)
57251	544	1236321	Human laminin gamma2 chain gene (LAMC2)
57253	545	213831	H. sapiens lysyl hydroxylase isoform 2 (PLOD2)
57254	546	536897	Human follistatin- related protein precursor mRNA
57257	548	339656	Human endothelial cell thrombomodulin
57258	549	190467	Human prion protein (PrP) mRNA
57261	551	338031	Human serglycin gene
57262	552	178430	Human alphoid DNA (alphoid repetitive sequence)
57265	555	4502562	H. sapiens calpain, large polypeptide L2 (CAPN2)
57266	556	398163	H. sapiens mRNA for insulin- like growth factor binding protein- 3
57269	559	7262375	H. carboxylesterase 2 (intestine, liver) (CES2)
57272	562	467560	H. sapiens mRNA for cysteine

Clone	SEQ ID NO:	GenBank Accession	Description
			dioxygenase type 1
57274	563	482664	H. sapiens annexin A3 (ANXA3)
57275	564	2281904	H. sapiens Bruton's tyr. kinase (BTK), alpha- D- galactosidase A (GLA)
57277	565	4557498	H. sapiens C- terminal binding protein 2 (CTBP2)
57282	568	189245	Human, NAD(P) H: menadione oxidoreductase mRNA
57287	571	28525	Human mRNA for amyloid A4 precursor of Alzheimer's disease
57288	572	4757755	H. sapiens annexin A2 (ANXA2)
57289	573	5729841	H. sapiens glyoxalase I (GLO1) mRNA
57290	574	6103642	H. sapiens F- box protein FBX3 mRNA
57295	576	182513	Human ferritin L chain mRNA
57299	579	37137	Human mRNA for thrombospondin
57301	580	179682	Human (clone A12) C4b- binding protein beta- chain
57302	581	6042205	H. sapiens membrane metallo-endopeptidase (neutral endopeptidase,enkephalinase, CALLA, CD10) (MME)
57213	517	2665791	H. sapiens caveolin- 2 mRNA
57259	550	2665791	H. sapiens caveolin- 2 mRNA
57225	523	179765	Human calcyclin gene
57229	526	179765	Human calcyclin gene
57237	534	186962	Human laminin B2 chain gene
57249	542	186962	Human laminin B2 chain gene
57231	528	4972626	H. sapiens caveolin 1 (CAV1) gene
57296	577	4972626	H. sapiens caveolin 1 (CAV1) gene
57297	578	4972626	H. sapiens caveolin 1 (CAV1) gene
57240	537	266237	insulin- like growth factor binding protein 3
57292	575	184522	Human insulin- like growth factor-binding protein- 3 gene
57263	553	4504618	H. sapiens insulin- like growth factor binding protein 7 (IGFBP7)
57280	566	4504618	H. sapiens insulin- like growth factor binding protein 7 (IGFBP7)
Homology to Ribosomal Protein			
57209	513	337504	Human ribosomal protein S24 mRNA

Example 10

Isolation and Characterization of T Cell Receptors from T Cell Clones Specific for Lung Tumor Antigens

This example describes the cloning and sequencing of T cell receptor (TCR) alpha and beta chains from a CD8 T cell clone specific for an antigen expressed by the lung tumor cell line LT391-06. T cells have a limited lifespan. Cloning of TCR chains and subsequent transfer would essentially enable infinite propagation of the T cell specificity. Cloning of tumor antigen TCR chains allows the transfer of the specificity into T cells isolated from patients that share TCR MHC-restricting alleles. Such T cells can then be expanded and used in adoptive transfer techniques to introduce the tumor antigen specificity into patients carrying tumors that express the antigen (see, for example, Clay et al. *J. Immunol. 163*:507 (1999)).

Cytotoxic T lymphocyte (CTL) clones specific for the lung tumor cell line LT391-06 were generated. Total mRNA from 2 x 10^6 cells from 15 such clones was isolated using Trizol reagent and cDNA was synthesized using Ready-to-Go kits (Pharmacia). To determine Va and Vb sequences in these clones, a panel of Va and Vb subtype-specific primers was synthesized and used in RT-PCR reactions with cDNA generated from each of the clones. The RT-PCR reactions demonstrated that each of the clones expressed a common Vb sequence that corresponded to the Vb13 subfamily. Using cDNA generated from one of the clones (referred to as 1105), the Va sequence expressed was determined to be Va22. To clone the full TCR alpha and beta chains from clone 1105, primers were designed that spanned the initiator and terminator-coding TCR nucleotides. Standard 35-cycle RT-PCR reactions were established using cDNA synthesized from the CTL clone and the primers, with PWO (BMB) as the thermostable polymerase. The resultant specific bands (approximately 850 bp for the alpha chain and approximately 950 bp for the beta chain) were ligated into the PCR blunt vector (Invitrogen) and transformed into *E. coli*. *E. coli* transformed with plasmids containing the full-length alpha and beta chains were identified, and large scale preparations of the corresponding plasmids were generated. Plasmids containing full-length TCR alpha and beta chains were sequenced. The determined cDNA sequences for the alpha and beta chains are provided in SEQ ID NO: 583 and 582, respectively, with the corresponding amino acid sequences being provided in SEQ ID NO: 584 and 585, respectively.

Example 11

CLONING OF cDNAs ENCODING LUNG SMALL CELL CARCINOMA ANTIGENS

Lung small cell carcinoma antigens were cloned by screening a small cell cDNA expression library with a mouse anti-SCID mouse serum. This antiserum was developed by growing lung small cell carcinoma cell lines NCIH69 and NCIH128 in SCID mice, removing SCID serum containing shed and secreted tumor antigens and immunizing normal mice with this serum. The library was constructed with mRNA from cell line NCIH128 in the lambda ZAP Express expression vector (Stratagene). The antiserum was adsorbed with *E. coli* lysate and human GAPDH protein and Ku autoantigens, and human PBMC lysate was added to the serum to block antibody to proteins found in normal tissue.

Sixty clones were isolated and the inserts of these clones were sequenced. The isolated clones and their respective sequence and clone identifiers are presented in Tables 6 and 7. The isolated clone sequences were compared to sequences in publically available databases. A summary of the Genbank homologies is found in Tables 6 and 7. Those showing some degree of similarity with known sequences are described in Table 6, while those showing little or no similarity with known sequences are described in Table 7.

TABLE 6

SEQ ID NO:.	CLONE ID #	Genbank Homologies
589	54534	Homo sapiens mRNA for LAK-1
590	54536	Homo sapiens CGI-108 protein mRNA
591	54538	Human mRNA for HHR23A protein
592	54540	Homo sapiens chromosome 17, clone hRPC. 1030_0_14
593	55084	Homo sapiens homolog of rat elongation factor p18 (p18)
594	55086	Homo sapiens HSPC194 mRNA
595	54555	Homo sapiens accessory proteins BAP31/BAP29 (DXS1357E) mRNA
596	54557	Homo sapiens mesenchymal stem cell protein DSCD75 mRNA
597	54564	Homo sapiens prp28, U5 snRNP 100 kd protein (U5-100K) mRNA
599	55473	Homo sapiens uroporphyrinogen III synthase (congenital erythropoietic porphyria) (UROS
600	55104	Homo sapiens carbonyl reductase (LOC51181)
601	55105	Homo sapiens membrane component, chromosome 11,

SEQ ID NO:.	CLONE ID #	Genbank Homologies
		surface marker 1 (M11S1)
602	55107	H.sapiens mRNA encoding GPI-anchored protein p137
604	55114	Homo sapiens mRNA; cDNA DKFZp56401716
605	55477	H.sapiens YB-1 gene promoter region
606	55482	Homo sapiens mRNA ; cDNA DKFZp434B0425
607	55483	Human Gu protein mRNA
608	55485	Homo sapiens 45kDa splicing factor mRNA
609	55487	Homo sapiens genomic DNA, chromosome 21q, section 72/105
610	55488	Homo sapiens chromosome 17, clone hCIT529l10
612	55089	Homo sapiens scaffold attachment factor A (SAF-A) mRNA
613	55092	Homo sapiens density regulated protein drp1 mRNA
614	55093	H.sapiens mRNA encoding GPI-anchored protein p137
615	56926	Homo sapiens high-mobility group (nonhistone chromosomal) protein 17 (HMG17)
617	56944	Homo sapiens KBNA-2 co-activator (100kD) (p100), mRNA
619	55490	Homo sapiens death-associated protein 6 (DAXX) mRNA, and translated products.
620	55495	Homo sapiens mRNA for MEGF6
621	55504	Mus musculus hairy / enhancer of split 6 mRNA
624	56482	H.sapiens DNA from chromosome 19-cosmids R31158, R31874, & R28125, genomic seq.
626	56487	Human L23 mRNA for putative ribosomal protein
627	56488	Homo sapiens cDNA FLJ10526 fis, clone NT2RP2000931, highly similar to MATRIN 3
628	56490	Homo sapiens Sul1 isolog mRNA
630	56494	Homo sapiens mRNA; cDNA DKFZp564B167 (from clone DKFZp564B167)
631	56495	Homo sapiens 12p13.3 BAC RPCl11-543P15 (Roswell Park Cancer Inst. Human BAC lib.)
632	56499	Human DNA-binding protein B (dbpB) gene, 3' end
633	56517	Homo sapiens esterase D mRNA
634	56952	Homo sapiens 14q32 Jagged2 gene, complete cds; and unknown gene
635	56953	Homo sapiens DNA polymerase zeta catalytic subunit (REV3L) mRNA
637	57139	Homo sapiens ribosomal protein, large, PO (RPLPO) mRNA
638	57078	Homo sapiens alpha-tubulin isoform 1 mRNA

SEQ ID NO:.	CLONE ID #	Genbank Homologies
640	57099	Homo sapiens uncharacterized hypothalamus protein HBEX2 mRNA
642	57105	Homo sapiens splicing factor, arginine/serine-rich 7 (35kD) (SFRS7)
643	57111	Human chromosome 14 DNA sequence
644	57117	Human DNA sequence from cosmid V857G56, between markers DXS366 and DXS87 on chromosome X contains ESTs
645	57121	Homo sapiens genomic DNA of 8p21.3-p22 anti-oncogene of hepatocellular colorectal and non-small cell lung cancer, segment 3/11
646	57124	H.sapiens MLN50 mRNA
647	57125	Homo sapiens calreticulin (CALR) , mRNA

Table 7

SEQ ID NO:.	CLONE ID #	Genbank Homologies
588	54533	Novel
598	55098	Novel
603	55108	Novel
611	55087	Novel (partial overlap of Unknown: Homo sapiens partial mRNA, clone c1-10e16)
616	56930	Novel
618	56945	Novel
622	55506	Novel / (136bp: Mus musculus mRNA for Rab24 protein)
623	56480	Novel
625	56484	Novel
629	56493	Novel
636	56959	Novel
639	57092	Novel
641	57100	Novel (last 120 bp: Unknown: Canine 21 kDa Signal peptase subunit mRNA)

In further studies, the expression levels of certain of these disclosed isolated antigens were compared to the expression levels in 36 normal tissues using microarray technology and computer analysis. These sequences were arrayed on Chip #7. The results of these studies are shown below in Table 8.

TABLE 8

Clone Name	Clone ID #	SEQ ID NO:	Squa/N	Aden/N	SC/N
LSCC2-1	54533	588	3	2	1
LSCC2-2	54534	589	5	3	5
LSCC2-4	54536	590	3	2	2
LSCC2-8	54540	592	0	3	2
LSCC2-18	55084	593	2	2	1
LSCC2-23	54555	595	2	3	3
LSCC2-25	54557	596	2	1	1
LSCC2-32	54564	597	2	3	2
LSCC2-48	55473	599	4	2	1
LSCC2-58	55104	600	3	5	2
LSCC2-61	55107	602	2	5	3
LSCC2-75	55483	607	2	4	2
LSCC2-79	55487	609	3	2	2
LSCC2-93	55089	612	5	4	4
LSCC2-121	55490	619	4	2	2
LSCC2-127	55495	620	2	4	1
LSCC2-137	55504	621	0	3	8
LSCC2-139	55506	622	3	4	1
LSCC2-161	56480	623	3	2	1
LSCC2-164	56482	624	2	4	2
LSCC2-171	56488	627	6	4	5
LSCC2-178	56494	670	3	5	3
LSCC2-191	56517	673	5	2	2

Squa/N = fold overexpression in squamous lung tumor versus normal tissues
Aden/N = fold overexpression in adenocarcinoma versus normal tissues
SC/N = fold overexpression in lung small cell carcinoma versus normal tissues

Example 12

USE OF MOUSE ANTISERA TO IDENTIFY cDNA SEQUENCES ENCODING LUNG SMALL CELL CARCINOMA ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung small cell carcinoma antigens by screening a small cell carcinoma cell line cDNA library with mouse anti-SCID mouse sera.

A directional cDNA expression library was constructed with mRNA from small cell carcinoma cell line NCIH128 employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Sera was obtained from SCID mice

containing human small cell carcinoma cell lines NCIH69 and NCIH128. The sera contains shed and secreted tumor antigens. These sera were pooled and injected into normal mice to produce anti-SCID mouse sera. The antiserum was absorbed with *E. coli* lysate, human GADPH protein and Ku autoantigens, and human PBMC lysate was added to the serum to block antibodies to proteins found in normal tissue.

Thirty-nine clones were isolated and the inserts of these clones were sequenced. The isolated clones and their respective sequence and clone identifier are presented in Table 9. The clone sequences were compared to sequences in publicly available databases (Geneseq, GenBank and huESTdb). A summary of these comparisons are found in Tables 10 and 11. Those showing some degree of homology with known sequences are described in Table 10, while those showing little or no similarity to known sequences are described in Table 11.

TABLE 9

CLONE NAME	SEQ. ID. NO:	CLONE ID #
LSCC-8	648	50664
LSCC-13	649	50669
LSCC-18	650	50673
LSCC-25	651	50680
LSCC-33	652	50685
LSCC-47	653	50699
LSCC-48	654	50700
LSCC-50	655	50702
LSCC-52	656	50704
LSCC-58	657	50710
LSCC-59	658	50711
LSCC-67	659	50719
LSCC-68	660	50720
LSCC-73	661	50725
LSCC-75	662	50727
LSCC-77	663	50729
LSCC-84	664	50736
LSCC-86	665	50738
LSCC-88	666	50740
LSCC-89	667	50741
LSCC-92	668	50744
LSCC-93	669	50745
LSCC-103	670	50754
LSCC-105	671	50756
LSCC-106	672	50757
LSCC-110	673	50761

CLONE NAME	SEQ. ID. NO:	CLONE ID #
LSCC-112	674	50763
LSCC-116	675	50767
LSCC-145	676	50775
LSCC-146	677	50776
LSCC-147	678	50777
LSCC-156	679	50786
LSCC-157	680	50787
LSCC-159	681	50789
LSCC-167	682	51003
LSCC-171	683	51007
LSCC-178	684	51014
LSCC-207	685	51304
LSCC-239	686	51568

TABLE 10

Seq. ID. No.	GenBank (ACCESS. #)	Description
648	D21094	Human mRNA for motor protein
652	NM_004487	Homo sapiens golgi autoantigen, golgin subfamily b, macrogolgin w/transmembrane signal
653	J04031	Human methylenetetrahydrofolate dehydrogenase-methenyltetrahydrofolate cyclohydrolase-formyltetrahydrofolate synthetase mRNA
654	MN_007086	Homo sapiens AND-1 protein (AND-1), mRNA
657	J03483	Human chromogranin A mRNA
658	AF191340	Homo sapiens anaphase-promoting complex subunit 7 (APC7)
661	AC020663	Homo sapiens chromosome 16 clone RPC1-11_127120
662	D13388	Human mRNA for DnaJ protein homolog
663	AB014540	Homo sapiens mRNA for KIAA0640 protein, partial cds
666	NM_005898	Homo sapiens membrane component, chromosome 11, surface marker 1 (M11S1)
667	X75304	H.sapiens giantin mRNA
668	Z29067	H.sapiens AF-1p mRNA
669	AJ133129	H.sapiens mRNA for small glutamine-rich tetratricopeptide repeat containing protein
670	AF058918	Homo sapiens unknown mRNA
671	D89976	H.sapiens mRNA for 5-aminoimidazole-4-carboxamide ribonucleotide transformylase
672	NM_001539	Homo sapiens heat shock protein, DNAJ-like 2 (HSJ2) mRNA
673	AC020663	Homo sapiens chromosome 16 clone RPCI-11-127I20
674	D21235	Human mRNA for HHR23A protein

Seq. ID. No.	GenBank (ACCESS. #)	Description
676	MN_003804	Homo sapiens receptor (TNFRSF)-interacting serine-threonine kinase 1 (RIPK1)
677	X76180	H.sapiens mRNA for lung amiloride sensitive Na+ channel Protein
678	AB018330	Homo sapiens mRNA for KIAA0787 protein, partial cds
	U87803	Human putative ca2+/calmodulin-dependent protein kinase gene, 3′ flanking region
679	L31610	Homo sapiens (clone cori-1c15) S29 ribosomal protein mRNA
680	Z83840	Human DNA sequence from clone CTA-216E10 on chromosome 22 contains the NHP2L1 gene for non-histone chromosome protein 2
682	D14696	Human mRNA for KIAA0108 gene
683	Z47087	H.sapiens mRNA for RNA polymerase II elongation factor-like protein
684	Z83840	Human DNA sequence from clone CTA-216E10 on chromosome 22 contains the NHP2L1 gene
685	U01923	Human BTK region clone ftp-3 mRNA

TABLE 11

Seq. ID. No.	GenBank (ACCESS. #)	Description
649		Novel
650	AC005023	Unknown: Homo sapiens BAC clone GS1-421I3 from Xq25-q26
651		Novel
655	AC007199	Unknown: Homo sapiens chromosome 5 BAC clone 111n13
656	AC005988	Unknown: Homo sapiens chromosome 17, clone hRPK.299_G_24
659	AK001695	Unknown: Homo sapiens cDNA FLJ10833 fis, clone NT2RP4001206, moderately similar to Drosophila melanogaster strawberry notch mRNA
660	AK001722	Unknown: Homo sapiens cDNA FLJ10860 fis, clone NT2RP4001568, weakly similar to ZINC FINGER PROTEIN GCS1
664	AK001925	Unknown: Homo sapiens cDNA FLJ11063 fis, clone PLACE1004814, weakly similar to SPLICING FACTOR, ARGININE/SERINE-RICH 4
665		Novel
675	(AJ131096)	Novel (1 to 103 bp is Picea abies microsatellite RNA), clone PAAG2

Seq. ID. No.	GenBank (ACCESS. #)	Description
681	AP001065	Unknown: Homo sapiens genomic DNA, chromosome 21, clone:KB68A7, MX-D21S171 region
686		Novel

In further studies, the expression levels of certain of these disclosed isolated antigens were compared to the expression levels in 36 normal tissues using microarray technology and computer analysis. These sequences were arrayed on Chip #7. The results of these studies are shown below in Table 12.

TABLE 12

Clone Name	Clone ID #	SEQ ID NO:	Squa/N	Aden/N	SC/N
LSCC-8	50664	648	4	3	2
LSCC-13	50669	649	2	4	0
LSCC-59	50711	658	4	2	3
LSCC-84	50736	664	6	3	4
LSCC-86	50738	665	1	4	0
LSCC-88	50740	666	2	3	4
LSCC-92	50744	668	3	1	1
LSCC-105	50756	671	4	3	2
LSCC-106	50757	672	4	3	1
LSCC-110	50761	673	8	3	4
LSCC-146	50776	677	3	1	1
LSCC-147	50777	678	5	2	3
LSCC-156	50786	679	4	2	2
LSCC-159	50789	681	2	2	1
LSCC-171	51007	683	2	1	1
LSCC-207	51304	685	3	4	3
LSCC-239	51568	686	4	3	2

Squa/N = Squamous lung tumor versus Normal tissues
Aden/N = Adenocarcinoma over versus tissues
SC/N = Lung Small Cell carcinoma versus Normal tissues

Example 13

USE OF MOUSE ANTISERA TO IDENTIFY cDNA SEQUENCES ENCODING LUNG SMALL CELL CARCINOMA ANTIGENS

This example illustrates the isolation of cDNA sequences encoding lung small cell carcinoma antigens by screening a small cell carcinoma cell line cDNA library with mouse anti-SCID mouse sera.

A directional cDNA expression library was constructed with mRNA from a SCID-passaged human lung cancer tumor DMS79 employing the Lambda ZAP Express expression system (Stratagene, La Jolla, CA). Sera was obtained from SCID mice containing the human lung cancer tumors DMS79 and NCIH688. The sera contains shed and secreted tumor antigens. These sera were pooled and injected into normal mice to produce anti-SCID mouse sera. The antiserum was absorbed with *E. coli* lysate, human GADPH protein and Ku autoantigens, and human PBMC lysate was added to the serum to block antibodies to proteins found in normal tissue.

Forty-one clones were isolated and the inserts of these clones were sequenced. The isolated clones and their respective sequence identifiers are presented in Table 13. The clone sequences were compared to sequences in publicly available databases. A summary of these comparisons are found in Tables 14 and 15. Those showing some degree of similarity with known sequences are described in Table 14, while those showing little or no similarity to known sequences are found in Table 15.

TABLE 13

CLONE NAME	SEQ. ID. NO:.	CLONE ID #
DMS-3	687	48564
DMS-8	688	48567
DMS-9	689	48568
DMS-12	690	48571
DMS-14	691	45572
DMS-25	692	48578
DMS-35	693	48583
DMS-38	694	48584
DMS-39	695	48585
DMS-47	696	49059
DMS-50	697	49061
DMS-53	698	49065
DMS-61	699	49070
DMS-63	700	49072
DMS-64	701	49073
DMS-67	702	49076

CLONE NAME	SEQ. ID. NO:.	CLONE ID #
DMS-75	703	50793
DMS-76	704	50794
DMS-79	705	50797
DMS-84	706	50800
DMS-93	707	50805
DMS-126	708	50984
DMS-129	709	50986
DMS-139	710	51065
DMS-151	711	51070
DMS-164	712	51078
DMS-168	713	51080
DMS-175	714	51084
DMS-193	715	51095
DMS-199	716	51099
DMS-200	717	51100
DMS-204	718	51103
DMS-214	719	51112
DMS-218	720	51113
DMS-221	721	51116
DMS-232	722	51123
DMS-253	723	51212
DMS-270	724	51220
DMS-275	725	51224
DMS-289	726	51234
DMS-296	727	51239

TABLE 14

SEQ ID NO:	GenBank
687	KIAA0013:cDNA from Hu. BM myeloblast line
688	Hu. Homolog Mu. LLRep3, sim. To ribosomal S2
689	KIAA0769, Hu. brain protein
690	Hu. Thymidylate kinase (CDC9), regul'n
691	Hu. Ku automimmune Ag; Nuc. Fctr. IV
692	Hu. Polyubiquitin UbC
693	Hu. FLJ20423 fis (signet-ring cell carc. Celline)
694	KIAA0640, SWAP-70 (Hu, brain protein)
695	Human radixin (cytosleletal)
696	Hu. Ribosomal protein L13a
697	Hu. trk oncogene, cytoskltl. Tropomyosin
698	DKFZp586K2120 (uterus) KIAA0784 (brain)
699	Hu. Chromogranin A (parathyr. Secrtry. Pro. 1)
700	Hu. Glutathione-S-transferase homolog
701	Hu. lactate dehydrogenase-A

SEQ ID NO:	GenBank
702	Hu.GPI-anchored membr. Pro. p137
704	Hu. HMG-17
705	Hu. Ubiquitin C-terminal hydrolase (UHX1)
706	Hu. Cosmid 25, PAC clone RP5-901A4
707	Hu. lactate dehydrogenase B
708	Hu. NuMA gene
709	Hu. KIAA0008 gene
710	Hu. BCL2/adenovirus E1B pro.2 (BNIP2)
711	Hu. Unactive progesterone receptor P23
712	Hu. alpha II spectrin
713	Hu. Transcriptional coactivator ALY
714	Hu. DnaJ Heat Shock homolog
715	Hu. mitoch. Or Replication
716	Hu. Ornithine decarboxylase antizyme (brain)
717	Hu. Deoxycytidine kinase
718	Hu. Fumarase
719	Hu. 80K-H protein (kinase C substrate)
721	Hu. Neuro-d4 (rat) homolog
722	Hu. Sodium/glucose cotransporter, repeat
724	Hu. Zinc finger protein ZNF226
725	Hu. Jumping transloc'n brkpt. Gene
726	Hu. M-phase phosphoprotein
727	Hu. Peroxisomal signal receptor 1

TABLE 15

SEQ ID NO:	GenBank
703	Novel
720	Novel (ALU?)
723	Novel

Example 14

ANALYSIS OF cDNA EXPRESSION USING MICROARRAY TECHNOLOGY

In additional studies, four clones obtained in Example 13 were found to be overexpressed in specific tumor tissues as determined by microarray analysis. Using this approach, cDNA sequences are PCR amplified and their mRNA expression profiles in tumor and normal tissues were examined using cDNA microarray technology essentially as described (Shena *et al.*, 1995). In brief, the clones are arrayed onto glass slides as multiple replicas, with each location corresponding to a unique cDNA clone (as many as 5500 clones can be arrayed on a single slide, or chip). Each chip is

hybridized with a pair of cDNA probes that are fluorescence-labeled with Cy3 and Cy5, respectively. Typically, 1μg of polyA$^+$ RNA is used to generate each cDNA probe. After hybridization, the chips are scanned and the fluorescence intensity recorded for both Cy3 and Cy5 channels. There are multiple built-in quality control steps. First, the probe quality is generally monitored using a panel of ubiquitously expressed genes. Secondly, the control plate also can include yeast DNA fragments of which complementary RNA may be spiked into the probe synthesis for measuring the quality of the probe and the sensitivity of the analysis. Currently, the technology offers a sensitivity of about 1 in 100,000 copies of mRNA. Finally, the reproducibility of this technology can be ensured by including duplicated control cDNA elements at different locations.

The extended predicted full length sequences for partial sequences of clones, DMS39, DMS126, DMS218 and DMS253 (previously isolated in Example 13) were obtained from the GenBank databases after database searches using the original partial cDNA sequences as the query. The predicted full length sequences for the cloned cDNA sequence for clones DMS39, DMS126, DMS218 and DMS253 are provided in SEQ ID NO:728-731, respectively. SEQ ID NO:728-731 were analyzed by comparison to sequences in the publicly available databases. A summary of these comparisons is presented in Table 16.

TABLE 16

SEQ ID NO:	Clone Name	Blastn
728	DMS-39	Human radixin
729	DMS-126	Human nuclear mitotic apparatus protein
730	DMS-218	Hu. cDNA: FLJ21840 fis; XPMC2
731	DMS-253	Hu. mRNA for KIAA1582 protein

Example 15

ANALYSIS OF cDNA EXPRESSION USING MICROARRAY TECHNOLOGY

In an additional study, a clone obtained in Example 12 was found to be overexpressed in specific tumor tissues as determined by microarray analysis. Using this approach, the cDNA sequence is PCR amplified and its mRNA expression profiles in tumor and normal tissues was examined using cDNA microarray technology as described in Example 13. Microarray analysis showed the cDNA for LSCC-86 is strongly overexpressed in small cell carcinoma cell line HTB 173; moderately overexpressed in atypical carcinoid METs, adenocarcinoma lung tumors and squamous

lung tumors; and slightly overexpressed in primary small cell. This cDNA is also strongly overexpressed in pituitary gland; moderately overexpressed in brain and adrenal gland; and slightly overexpressed in skeletal muscle.

Clone LSCC-86 was originally isolated in Example 12 and a partial sequence of this insert is provided in SEQ ID NO:665. An extended sequence was obtained by PCR sequencing using internal primer sequences designed from the partial cDNA sequence of clone LSCC-86. This extended sequence represents the full-length sequence for the cloned cDNA sequence of clone LSCC-86. The determined full length sequence for LSCC-86 is provided in SEQ ID NO:732. SEQ ID NO:732 was analyzed by comparison to sequences in the publicly available databases. Database searches showed no homology in GenBank, seven ESTs (3 lung tumor and 4 uncatagorized hits) in the human EST database, and no homology in Blastx. Three open reading frames (ORFs) were identified. A first that encodes a protein with a sequence of 50 amino acid residues (SEQ ID NO:733) which is fused to LacZ. A second that encodes a protein with a sequence of 76 amino acids residues (SEQ ID NO:734) which shows no homology in the databases. A third that encodes a protein with a sequence of 74 amino acid residues (SEQ ID NO:735) which also shows no homology in the databases. However, a motif search of SEQ ID NO:735 shows a possible small cytokine signature.

Example 16

Quantitative Real-time PCR Analysis using cDNAs Identified by T-cell Expression Cloning

In this Example, the nucleic acid sequence of the cDNA inserts contained in clones L86S-39 and L86S-47 (SEQ ID NOs:89 and 90), identified by T-cell (*i.e.*, serological) expression cloning, were used in Real-time PCR mediated expression analysis of a variety of tissues, including lung tumor, normal lung and other normal tissue samples.

Briefly, the first-strand cDNA was synthesized from 20μg of total RNA that had been treated with DNase I (Amplification Grade, Gibco BRL Life Technology, Gaitherburg, MD), using Superscript Reverse Transcriptase (RT) (Gibco BRL Life Technology, Gaitherburg, MD). Real-time PCR is performed with a GeneAmp™ 5700 sequence detection system (PE Biosystems, Foster City, CA). The 5700 system uses SYBR™ green, a fluorescent dye that only intercalates into double stranded DNA, and a set of gene-specific forward and reverse primers. The increase in fluorescence is monitored throughout amplification process. The optimal concentration of primers was determined using a pool of cDNAs from lung tumors, according to procedures known to

those of ordinary skill in the art. The PCR reaction was performed in 25µl volumes that include 2.5µl of SYBR green buffer, 2µl of cDNA template and 2.5µl each of the forward and reverse primers for the gene of interest. The cDNAs used for RT reactions are diluted 1:10 for each gene of interest and 1:100 for the β-actin control. In order to quantitate the amount of specific cDNA (and hence initial mRNA) in the sample, a standard curve is generated for each run using the plasmid DNA containing the gene of interest. Standard curves are generated using the Ct values determined in the Real-time PCR, which are related to the initial cDNA concentration used in the assay. Standard dilutions ranging from 20-2x10^6 copies of the gene of interest are used for this purpose. In addition, a standard curve is generated for β-actin ranging from 200fg-2000fg. This enables standardization of the initial RNA content of a tissue sample to the amount of β-actin for comparison purposes. The mean copy number for each group of tissues tested is normalized to a constant amount of β-actin, allowing the evaluation of the overexpression levels seen with each of the genes.

Real-time PCR analysis performed as described above demonstrated that mRNAs corresponding to the cDNA inserts contained in clones L86S-39 and L86S-47 are overexpressed in 2 out of 6 squamous lung tumors and in 2 out of 4 head and neck tumors, with lower levels of expression detected in an additional 3 squamous and in 2 head and neck tumors. Little or no expression was detected in normal lung tissue. Some expression was detected in soft palate, tonsil, trachea, esophagus, salivary gland, bronchus and cervix.

Example 17

Identification of an Extended Polynucleotide Sequence and Corresponding Amino Acid Sequence For cDNA Inserts Contained in Lung Tumor Clones L86S-39 and L86S-47

This Example describes the determined extended nucleic acid sequence for the full-length cDNA inserts contained in clones L86S-39 and L86S-47, corresponding to lung tumor antigens identified by T-cell (*i.e.*, serological) expression cloning.

A determined 5' polynucleotide sequence of the cDNA insert contained in clone L86S-47 has been disclosed in SEQ ID NO:90, which corresponds to the amino acid sequence set forth in SEQ ID NO:99. In this Example, an extended nucleic acid sequence of the full-length insert contained in clone L86S-47 has been determined, as disclosed in SEQ ID NO:736. The amino acid sequence of a corresponding open reading frame contained therein is provided in SEQ ID NO:738.

The determined 5' polynucleotide sequence of the cDNA insert contained in clone L86S-39 has been disclosed in SEQ ID NO:89, which corresponds to the amino acid sequence set froth in SEQ ID NO:98. In this Example, an extended nucleic acid sequence of the full-length insert contained in clone L86S-39 has been determined, as disclosed in SEQ ID NO:737. The deduced amino acid sequence of a corresponding open reading frame contained therein is provided in SEQ ID NO:739.

In view of the lung tumor-associated expression profile of these sequences, the nucleic acid and/or amino acid sequences as described above can be used, for example, in a variety of diagnostic and/or therapeutic applications associated with lung cancer, illustrative examples of which are described hereinabove.

Example 18

PCR Cloning and Identification of an Extended cDNA Encoding a Full-Length L200T Polypeptide

In this Example, an extended cDNA sequence (SEQ ID NO:740), related to the polynucleotide identified in Example 8 (SEQ ID NO:440), was identified using an approach which combined (i) anchored PCR mediated subcloning and nucleic acid sequence determination, with (ii) sequence analysis of an overlapping human genomic DNA (gDNA) clone. This analysis was used to assemble the extended nucleic acid sequence identified in SEQ ID NO:740, including an extended open reading frame (SEQ ID NO:741) encoding a full-length L200T polypeptide having an amino acid sequence disclosed in SEQ ID NO:742.

In Example 8, SEQ ID NO:440 was shown to be related to a nucleic acid sequence encoding a truncated human cystine/glutamate transporter (GenSeq No. Z16609; herein referred to as SEQ ID NO:743). However, unlike the published sequence of the human cystine/glutamate transporter, SEQ ID NO: 440 contains a unique 5' terminus of 181 nucleotides. As disclosed in Example 8, this novel 5' sequence results in the removal of the reported initiating methionine (start codon) along with an additional two amino acids of the published transporter protein sequence. Accordingly, the deduced translation product of SEQ ID NO:740 represents a polypeptide (*i.e.*, SEQ ID NO:742) encoded by a translation reading frame that is clearly distinct from that used to translate the cystine/glutamate transporter protein.

However, although SEQ ID NO:440 contains an ATG that could function as a translation initiation codon, no 5' inframe (upstream) stop codon was identified therein. Therefore, in order to further evaluate this open reading frame, anchored PCR mediated cloning of a cDNA library was used to identify cDNAs

containing additional 5' extended nucleic acid sequence, encoding additional amino terminal amino acids of the polypeptide referred to as L200T. Anchored PCR cloning identified an additional 47 nucleotides 5' of the first nucleotide of SEQ ID NO:440. This extended 5' nucleotide sequence disclosed in SEQ ID NO:744, is also contained in SEQ ID NO:740 (nucleotide positions 38-84). Accordingly, this analysis identified an ATG translation initiation codon that extends the deduced amino acid sequence of the open reading frame in SEQ ID NO:440 by an additional 16 amino acids, as set forth in SEQ ID NO:745.

Further analysis of L200T nucleic acid and deduced amino acid sequence proceeded as follows. The 5' extended sequence (SEQ ID NO:744), contained in SEQ ID NO:740, includes an ATG translation start codon that is further upstream and inframe with the ATG codon previously identified in SEQ ID NO:440. Using the 5' extended cDNA sequence contained in SEQ ID NO:744 and sequence contained in SEQ ID NO:440, bioinformatic analysis of a corresponding human genomic DNA sequence was used to identify an inframe stop codon upstream of the 5' most ATG translation start codon, as shown in the composite 5' extended cDNA sequence set forth in SEQ ID NO:740. Accordingly, the inframe stop codon (TGA) in SEQ ID NO:740 is identified by the T residue positioned 42 nucleotides 5' of the A of the translation initiation codon (ATG) of the full-length open reading frame sequence encoding L200T (SEQ ID NO:741), contained therein. The clone containing this overlapping genomic DNA (gDNA) sequence (nucleotides 1-37 of SEQ ID NO:740) providing an inframe stop codon is contained within human chromosome 4, as identified by Genbank Accession No. AC093903 (SEQ ID NO:746). In this manner, anchored PCR cloning coupled with examination of overlapping genomic DNA sequence was used to establish the extended 5' polynucleotide sequence according to SEQ ID NO:740, and to identify a full-length open reading frame disclosed in SEQ ID NO:741, which is predicted to encode a corresponding full-length amino acid sequence (SEQ ID NO:742), the full-length polypeptide referred to as L200T. Consistent with analysis of SEQ ID NO:440 (see Example 8), the full-length amino acid sequence of SEQ ID NO:742 contains the $CD8^+$ T-cell epitope of SEQ ID NO:587, which is reactive to the lung tumor cell line LT-391-06.

The extended nucleotide coding sequence contained in SEQ ID NO: 741 includes nucleotide sequence determined by anchored PCR from a cDNA library, while the inframe stop codon disclosed in SEQ ID NO:740 was identified by analysis of an overlapping gDNA sequence, as discussed above. Accordingly, the genomic nucleotide sequence (161,280 base pairs) of human chromosome 4 (GenBank Accession No.

AC093903), is disclosed in SEQ ID NO:746. In addition, a 17,672 nucleotide sequence derived from SEQ ID NO:746, which contains exon 1, intron 1 and exon 2 of L200T is provided in SEQ ID NO:747. The upstream inframe stop codon of SEQ ID NO:740, proximal to the 5' end of the anchored PCR cDNA nucleotide sequence, is located at nucleotide position 7,153 of SEQ ID NO:747. The "ATG" translation start codon (identified in SEQ ID NO: 741) is located at nucleotide position 7,195 of SEQ ID NO:747, and the anchored PCR cDNA sequence starts at nucleotide position 7,190. Therefore, L200T exon 1 encompasses nucleotides 7,153 through 7,426, intron 1 corresponds to nucleotides 7,427 through 17,403 and exon 2 begins at nucleotide 17,404. The L200T $CD8^+$ epitope (SEQ ID NO:587), as identified in Example 8, is encoded by nucleotide sequences 7,360 through 7,386, of SEQ ID NO:747.

Also identified in this analysis is a difference between the gDNA sequence and the anchored PCR cDNA sequence. This difference is identified as an "A" residue in the gDNA nucleotide sequence at position 7,198 of SEQ ID NO:747 and as a "G" residue at nucleotide position 4 of the extended open reading frame sequence (SEQ ID NO:741). This nucleotide sequence difference results in the deduced L200T amino acid of residue 2 being a Ser when referenced to gDNA sequence and Gly when referenced to the extended nucleotide sequence of SEQ ID NO:740. In addition, this analysis further identifies that the nucleic acid sequence encoding the human cysteine/glutamate transporter (GenSeq No. Z16609) starts at nucleotide position 17,134 of SEQ ID NO:747, which is located within intron 1 sequence of the L200T gene. Thus, the above analysis supports, as discussed in Example 8, that SEQ ID NO:740 and GenSeq No. Z16609 (SEQ ID NO:743) share overlapping nucleic acid sequence, however, encode distinctly different polypeptides, an L200T polypeptide and the cyctine/glutamate transporter, respectively.

Thus L200T nucleic acid and/or amino acid sequence, as described above, can be used in a variety of polynucleotide or polypeptide based diagnostic and/or therapeutic applications associated with lung cancer.

Example 19

EXPRESSION OF RECOMBINANT TRUNCATED L200T IN PROKARYOTIC HOST CELLS

In this example, an open reading frame contained in SEQ ID NO:440 identified in Example 8, which encodes an L200T polypeptide, was subcloned and recombinant protein expressed in *E. coli* host cells.

Briefly, an open reading frame of SEQ ID NO:440 was PCR amplified using the forward oligonucleotide primer

5'GAGGTTGAAGTGAGCAGAGATCATGCC 3' (SEQ ID NO:748) and reverse oligonucleotide primer 5' CTTACGAATTCATCAGCT-GCACTTTCTCCTGC 3' (SEQ ID NO:749). The PCR amplification using Pfu DNA polymerase (Stratagene, La Jolla, CA) was performed as follows: one cycle at 96°C for 2 minutes; 40 cycles of 96°C for 20 seconds, 62°C for 15 seconds, 72°C for 45 seconds; one cycle at 72°C for 4 minutes. The PCR product was digested with restriction endonuclease EcoRI and cloned (ligated) into the expression vector pPDM Trx2H (a modified pET28 vector that includes an inframe thioredoxin (Trx) encoding sequence flanked, both 5' and 3', with 6xHis tags) that had been digested with StuI and EcoRI. The ligation reaction was transformed into BLR (DE3) pLysS and HMS 174 pLysS competent bacteria (Novagen Inc., Madison, WS). Recombinant clones were identified, plasmid DNA prepared and the nucleotide sequence of the insert determined. Expression of the encoded recombinant 6xHis-Trx-6xHis-L200T polypeptide fusion protein of the expected size was confirmed in coomassie stained gels. In addition, the fusion protein described above also includes several protease cleavage sites (enterokinase, thrombin and XA) located between the second 6xHis sequence and L200T coding sequence that are useful in the analysis, purification and preparation of recombinant L200T polypeptide.

The PCR mediated subcloning of truncated L200T into the above-identified modified pET28 vector directs the expression of recombinant truncated L200T containing an amino terminal fusion with 6xhistidine epitope tags and thioredoxin (Trx). Accordingly, recombinant protein expressed in *E. coli* host cells may be detected with commercially available anti-thioredoxin antibody and/or anti-6xHistidine antibody. Addition of thioredoxin as part of the amino terminal fusion protein allowed for the expression of detectable levels of recombinant truncated L200T fusion protein in *E. coli* host cells.

Recombinant L200T produced in this manner can be used, for example, to prepare monoclonal and/or polyclonal antibodies, to detect antibodies in patient sera, and/or in a variety of other diagnostic and/or therapeutic applications associated with lung caner.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is Claimed:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of:

(a) sequences provided in SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746;

(b) complements of the sequences provided in SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746;

(c) sequences consisting of at least 20 contiguous residues of a sequence provided in SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746;

(d) sequences that hybridize to a sequence provided in SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746, under moderately stringent conditions;

(e) sequences having at least 75% identity to a sequence of SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746;

(f) sequences having at least 90% identity to a sequence of SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746; and

(g) degenerate variants of a sequence provided in SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746.

2. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of:

(a) sequences encoded by a polynucleotide of claim 1; and

(b) sequences having at least 70% identity to a sequence encoded by a polynucleotide of claim 1; and

(c) sequences having at least 90% identity to a sequence encoded by a polynucleotide of claim 1; and

(d) at least a portion of an amino acid sequence set forth in SEQ ID NOs: 742, 733, 734, 735, 745, 738 and 739.

3. An expression vector comprising a polynucleotide of claim 1 operably linked to an expression control sequence.

4. A host cell transformed or transfected with an expression vector according to claim 3.

5. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a polypeptide of claim 2.

6. A method for detecting the presence of a cancer in a patient, comprising the steps of:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with a binding agent that binds to a polypeptide of claim 2;

(c) detecting in the sample an amount of polypeptide that binds to the binding agent; and

(d) comparing the amount of polypeptide to a predetermined cut-off value and therefrom determining the presence of a cancer in the patient.

7. A fusion protein comprising at least one polypeptide according to claim 2.

8. An oligonucleotide that hybridizes to a sequence recited in SEQ ID NOs: 740, 588, 598, 603, 611, 616, 622, 625, 629, 636, 639, 641, 649-651, 655, 656, 659, 660, 664, 665, 675, 681, 686, 703, 720, 723, 732, 736, 737, 741, 744 and 746 under moderately stringent conditions.

9. A method for stimulating and/or expanding T cells specific for a tumor protein, comprising contacting T cells with at least one component selected from the group consisting of:

(a) polypeptides according to claim 2;

(b) polynucleotides according to claim 1; and

(c) antigen-presenting cells that express a polypeptide according to claim 2,

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

10. An isolated T cell population, comprising T cells prepared according to the method of claim 9.

11. A composition comprising a first component selected from the group consisting of physiologically acceptable carriers and immunostimulants, and a second component selected from the group consisting of:

(a) polypeptides according to claim 2;

(b) polynucleotides according to claim 1;

(c) polynucleotides having a sequence as provided in any one of SEQ ID NOs: 740, 589-597, 599-602, 604-610, 612-615, 617-621, 623, 624, 626-628, 630-635, 637, 638, 640, 642-648, 652-654, 657, 658, 661-663, 666-674, 676-680, 682-685, 687-702, 704-719, 721, 722, 724-731, 736, 737, 741, 744 and 746;

(d) antibodies according to claim 5;

(e) fusion proteins according to claim 7;

(f) T cell populations according to claim 10; and

(g) antigen presenting cells that express a polypeptide according to claim 2.

12. A method for stimulating an immune response in a patient, comprising administering to the patient a composition of claim 11.

13. A method for the treatment of a cancer in a patient, comprising administering to the patient a composition of claim 11.

14. A method for determining the presence of a cancer in a patient, comprising the steps of:

(a) obtaining a biological sample from the patient;

(b) contacting the biological sample with an oligonucleotide according to claim 8;

(c) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and

(d) compare the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence of the cancer in the patient.

15. A diagnostic kit comprising at least one oligonucleotide according to claim 8.

16. A diagnostic kit comprising at least one antibody according to claim 5 and a detection reagent, wherein the detection reagent comprises a reporter group.

17. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4+ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of: (i) polypeptides according to claim 2; (ii) polynucleotides according to claim 1; and (iii) antigen presenting cells that express a polypeptide of claim 2, such that T cell proliferate;

(b) administering to the patient an effective amount of the proliferated T cells,

and thereby inhibiting the development of a cancer in the patient.

SEQUENCE LISTING

<110> Corixa Corporation
Lodes, Michael J.
Wang, Tongtong
Fan, Liqun
Algate, Paul A.
McNeill, Patricia D.

<120> COMPOSITIONS AND METHODS FOR
THE THERAPY AND DIAGNOSIS OF LUNG CANCER

<130> 210121.47502PC

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ragtggcctg tccatcagca tgtttctcat ctactttgct tgtccagtcc actgtggtcc 240
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624, 631, 636, 640, 646, 658, 669, 690
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gccactggca ctcccagcct gggktaacag agccamgact ctkgccgaaa aaaaaraama 420
cgacggagaa nmagntctgt tattccatgg gaaattkgaa tttccttcyt tkaaatatct 480
taaaatnggt cctcctwaaa aaagttcggc tggggcccgk tggctcacat tttkttaycc 540
cycccccttt tggggarggc caarggccgg kttgawtnnc ccttgagggg ccanaactcc 600
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cagagggttc tgcaggatgt gctattttaa agcagctggg tgcaacttgt gaaaacggga 180
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ctgttatttt anatnccaca tatnttttt aatgctnaag catacaggtt gaatttctgg 360
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aattcattaa ctttgtggtt gaagggagca gcgtcngaaa ctgctttagc acagtgggag 180
gaaaacaaac agattcatct ccggaaacca aaggaaaggg tragtgggtt tttattagcc 240
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ggttccctgt ctcccatggg cgtcatttca tgttgtcctc tgccttcccc cagatattct 180
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462, 530
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tttgctgagc aatacaatta tttgtatatg ttacttttt ttctgtttgg ctnaaagatt 180
tgatatgagc tgaggaaaat gaagccntta ctgctatnag atctnatccc tttccaccac 240
ctttcaggga tnttggcact gcayatattc agaattcccc nnagtcgctn gtgataaaaa 300
tgtcttcaga gatggcagaa tatgtttcct ttggtacatg ttcattaaaa atatacacgt 360
gctcactact gtggatatgt atgtnttgac cgatnacaca ggctgattta gggaagagat 420

aaaagcacac ttngaattta ttagcctttc accnagacta anattctgaa attaagaatg 480
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ctaagaggna attctgaact catccccnna tgacctctcc cgaatmagaa tatctctggc 480
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aaa 543

<210> 12
<211> 329
<212> DNA
<213> Homo sapiens

<400> 12
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ggcaagacca taggtggggt gctgggaatc ctcggggccg gctggcaccc actcctggtg 180
ctcaagggag agacccactt gttcagatgc atrggcctca ggcggttcaa ggcrgtctta 240
gagccacaga gtcaaataaa aatcaatttt gagagaccac agcacctgct gctttgatcg 300
tgatgttcaa ggcaagttgc aagtcatcg 329

<210> 13
<211> 314
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 238, 244, 267, 273
<223> n = A,T,C or G

<400> 13
cgatgacttg cacccgggag ctgtgacagt ggcctggaag cagatggcag ccccgtcaag 60
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tacctgagcc tgacgcccga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 180
catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttcata ggttcccnac 240
tctnacccca cccacgggag cctgganctg cangatcccg ggggaagggt ctctctcccc 300
atcccaagtc atcg 314

<210> 14

<211> 691
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 20, 166, 186, 196, 361, 543, 546, 577, 581, 626, 636, 661
<223> n = A,T,C or G

<400> 14
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ycytcttcyt ttgsccmggt tcktcnaaac cacttngttr aattccccgg sccgcctkgc 660
nggtycaacc wttttgggaa mamcyccccc c 691

<210> 15
<211> 355
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 87, 146, 195, 333
<223> n = A,T,C or G

<400> 15
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tcaacctctt cctctgggtg ggagcaagcg tccagcaggg tgttgtccag agccttttca 300
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<210> 16
<211> 522
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 90, 205, 213, 240, 264, 381, 405, 410, 414, 417, 423, 429,
432, 480, 508
<223> n = A,T,C or G

<400> 16
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ttnatcctnc tntgtaatac ttcctatgtg acatttctct tccccttgga aacactgcan 480
attttaactg tgagtttgat ctcttctngt gttactggac tg 522

<210> 17
<211> 317
<212> DNA
<213> Homo sapiens

<400> 17
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gagaatggca aaattagttg ccttcgtcga gagtgcccct ctgatgaatg tggtgctggg 180
gtgtttatgg caagtcactt tgacagacat tattgtggca aatgttgtct gacccactgt 240
ttcaactaac cagaagacaa gtaactgtat gagttaatta aagacatgaa ctaaaaaaaa 300
aaaaaaaaaa actcgag 317

<210> 18
<211> 392
<212> DNA
<213> Homo sapiens

<400> 18
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agaagcccct gacccttat ttccgcttct tcatggagaa gcgggccaag tatgcgaaac 180
tccaccctca gatgagcaac ctggacctga ccaagattct gtccaagaaa tacaaggagc 240
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gagcgaaacc tggcccgatt cagggaggat caccccacc ttatccagaa tgccaagaat 360
cggacatccc agagaagccc caagaccccc cg 392

<210> 19
<211> 2624
<212> DNA
<213> Homo sapiens

<400> 19
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<210> 20
<211> 488
<212> DNA
<213> Homo sapiens

<400> 20
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cctaaccc 488

<210> 21
<211> 391
<212> DNA
<213> Homo sapiens

<400> 21
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tggcgattgc tgatgctttg ggcaaaatcc ctcagacagt cctgtggcgg tacactggaa 120
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ctgaagatct agaagatgct ctgaagagca g 391

<210> 22
<211> 1320
<212> DNA

<213> Homo sapiens

<400> 22
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<210> 23
<211> 633
<212> DNA
<213> Homo sapiens

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gaaagatgta aattagcaga aaaaaaactc gag 633

<210> 24
<211> 1328
<212> DNA
<213> Homo sapiens

<400> 24
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<210> 25
<211> 1758
<212> DNA
<213> Homo sapiens

<400> 25
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<210> 26
<211> 493
<212> DNA
<213> Homo sapiens

<400> 26
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tactcgctgc ctc 493

<210> 27
<211> 1331
<212> DNA
<213> Homo sapiens

<400> 27
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gcaacagcgg cagtcccctg cccaagttat cccactagct gattactata tcattgctgg 300
agtgatctat caggcaccag acttgggatc agttataaac tctagagtgc ttactgcagt 360
gcatggtatt cagtcagctt ttgatgaagc tatgtcatac tgtcgatatc atccttccaa 420
agggtattgg tggcacttca aagatcatga agagcaagat aaagtcagac ctaaagccaa 480
aaggaaagaa gaaccaagct ctatttttca gagacaacgt gtggatgctt tacttttaga 540
cctcagacaa aaatttccac ccaaatttgt gcagctaaag cctggagaaa agcctgttcc 600
agtggatcaa acaaagaaag aggcagaacc tataccagaa actgtaaaac ctgaggagaa 660
ggagaccaca aagaatgtac aacagacagt gagtgctaaa ggcccccctg aaaaacggat 720
gagacttcag tgagtactgg acaaaagaga agcctggaag actcctcatg ctagttatca 780
tacctcagta ctgtggctct tgagctttga agtactttat tgtaaccttc ttatttgtat 840
ggaatgcgct tatttttga aaggatatta ggccggatgt ggtggctcac gcctgtaatc 900
ccagcacttt gggaggccat ggcgggtgga tcacttgagg tcagaagttc aagaccagcc 960
tgaccaatat ggtgaaaccc cgtctctact aaaaatacaa aaattagccg ggcgtggtgg 1020
cgggcgccca tagtcccagc tactcgggag gctgagacag gagacttgct tgaacccggg 1080
aggtggaggt tgccctgagc tgattatcat gctgttgcac tccagcttgg gcgacagagc 1140
gagactttgt ctcaaaaaaa gaagaaaaga tattattccc atcatgattt cttgtgaata 1200
tttgttatat gtcttctgta acctttcctc tcccggactt gagcaaccta cacactcaca 1260
tgtttactgg tagatatgtt taaaagcaaa ataaaggtat tggtataaaa aaaaaaaaaa 1320
aaaaactcga g 1331

<210> 28
<211> 1333
<212> DNA
<213> Homo sapiens

<400> 28
cggcggtgga tatccgagac aatctgctgg gaatttcttg ggttgacagc tcttggatcc 60
ctattttgaa cagtggtagt gtcctggatt acttttcaga aagaagtaat ccttttttatg 120
acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc 180
agatggttgg aatcgagtac atccttttgc atgctcaaga gcccattctt ttcatcattc 240
ggaagcaaca gcggcagtcc cctgcccaag ttatcccact agctgattac tatatcattg 300
ctggagtgat ctatcaggca ccagacttgg gatcagttat aaactctaga gtgcttactg 360
cagtgcatgg tattcagtca gcttttgatg aagctatgtc atactgtcga tatcatcctt 420
ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 480
ccaaaaggaa agaagaacca agctctattt ttcagagaca acgtgtggat gctttacttt 540
tagacctcag acaaaaattt ccacccaaat ttgtgcagct aaagcctgga gaaaagcctg 600

ttccagtgga tcaaacaaag aaagaggcag aacctatacc agaaactgta aaacctgagg 660
agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 720
ggatgagact tcagtgagta ctggacaaaa gagaagcctg gaagactcct catgctagtt 780
atcatacctc agtactgtgg ctcttgagct ttgaagtact ttattgtaac cttcttattt 840
gtatggaatg cgcttatttt ttgaaaggat attaggccgg atgtggtggc tcacgcctgt 900
aatcccagca ctttgggagg ccatggcggg tggatcactt gaggtcagaa gttcaagacc 960
agcctgacca atatggtgaa accccgtctc tactaaaaat acaaaaatta gccgggcgtg 1020
gtggcgggcg cccatagtcc cagctactcg ggaggctgag acaggagact tgcttgaacc 1080
cgggaggtgg aggttgccct gagctgatta tcatgctgtt gcactccagc ttgggcgaca 1140
gagcgagact ttgtctcaaa aaagaagaaa agatattatt cccatcatga tttcttgtga 1200
atatttgtga tatgtcttct gtaacctttc ctctcccgga cttgagcaac ctacacactc 1260
acatgtttac tggtagatat gtttaaaagc aaaataaagg tatttgtata aaaaaaaaaa 1320
aaaaaaactc gag 1333

<210> 29
<211> 813
<212> DNA
<213> Homo sapiens

<400> 29
ctgagctgca cttcagcgaa ttcacctcgg ctgtggctga catgaagaac tccgtggcgg 60
accgagacaa cagccccagc tcctgtgctg gcctcttcat tgcttcacac atcgggtttg 120
actggcccgg ggtctgggtc cacctggaca tcgctgctcc agtgcatgct ggcgagcgag 180
ccacaggctt tggggtggct ctcctactgg ctcttttgg ccgtgcctcc gaggacccgc 240
tgctgaacct ggtatccccg ctggactgtg aggtggatgc ccaggaaggc gacaacatgg 300
ggcgtgactc caagagacgg aggctcgtgt gagggctact tcccagctgg tgacacaggg 360
ttccttacct cattttgcac tgactgattt taagcaattg aaagattaac taactcttaa 420
gatgagtttg gcttctcctt ctgtgcccag tggtgacagg agtgagccat tcttctctta 480
gaagcagctt aggggcttgg tggggtctgg agaaaattgt cacagacccc ataggtctcc 540
atctgtaagc tctgtccctt gtcctccacc ctggtcttta gagccacctc aggtcaccct 600
ctgtagtgag tgtacttcct gacccaggcc cttgctcaag ctggggctcc ctggggtgtc 660
taaccagccc tgggtagatg tgactggctg ttagggaccc cattctgtga agcaggagac 720
cctcacagct cccaccaacc cccagttcac ttgaagttga attaaatatg gccacaacat 780
aaaaaaaaaa aaaaaaaaaa aaaaaaactc gag 813

<210> 30
<211> 1316
<212> DNA
<213> Homo sapiens

<400> 30
caggcgccca gtcatggccc aagagacagc accaccgtgt ggcccagtct caaggggtga 60
cagtccaatc atagaaaaga tggaaaaaag gacatgtgcc ctgtgccctg aaggccacga 120
gtggagtcaa atatactttt caccatcagg aaatatagtt gctcatgaaa actgtttgct 180
gtattcatca ggactggtgg agtgtgagac tcttgatcta cgtaatacaa ttagaaactt 240
tgatgtcaaa tctgtaaaga aagagatctg gagaggaaga agattgaaat gctcattctg 300
taacaaagga ggcgccaccg tggggtgtga tttatggttc tgtaagaaga gttaccacta 360
tgtctgtgcc aaaaaggacc aagcaattct tcaagttgat ggaaaccatg gaacttacaa 420
attattttgc ccagaacatt ctccagaaca agaagaggcc actgaaagtg ctgatgaccc 480
aagcatgaag aagaagagag gaaaaaacaa acgcctctca tcaggccctc ctgcacagcc 540
aaaaacgatg aaatgtagta acgccaaaag acatatgaca gaagagcctc atggtcacac 600
agatgcagct gtcaaatctc cttttcttaa gaaatgccag gaagcaggac ttcttactga 660
actatttgaa cacatactag aaaatatgga ttcagttcat ggaagacttg tggatgagac 720
tgcctcagag tcggactatg aagggatcga gaccttactg tttgactgtg gattatttaa 780
agacacacta agaaaattcc aagaagtaat caagagtaaa gcttgtgaat gggaagaaag 840
gcaaaggcag atgaagcagc agcttgaggc acttgcagac ttacaacaaa gcttgtgctc 900
atttcaagaa aatggggacc tggactgctc aagttctaca tcaggatcct tgctacctcc 960
tgaggaccac cagtaaaagc tgttcctcag gaaaactgga tggggcctcc atgttctcca 1020

aggatcgagg aagtcttcct gcctaccctg cccaccccag tcaagggcag caacaccaga 1080
gctttgctca gccttaaatg gaatcttaga gctttctctt gcttctgcta ctcctacaga 1140
tggcctcatc atggtctcca ctcagtatta ataactccat cagcatagag caaactcaac 1200
actgtgcatt gcacactgtt accatgggtt tatgctcact atcatatcac attgccaata 1260
tttagcacac ttaataaatg cttgtcaaaa cccaaaaaaa aaaaaaaaaa ctcgag 1316

<210> 31
<211> 1355
<212> DNA
<213> Homo sapiens

<400> 31
cggcggtgga tatccgagac aatctgctgg gaatttcttg ggttgacagc tcttggatcc 60
ctattttgaa cagtggtagt gtcctggatt acttttcaga aagaagtaat ccttttttatg 120
acagaacatg taataatgaa gtggtcaaaa tgcagaggct aacattagaa cacttgaatc 180
agatggttgg aatcgagtac atccttttgc atgctcaaga gcccattctt ttcatcattc 240
ggaagcaaca gcggcagtcc cctgcccaag ttatcccact agctgattac tatatcattg 300
ctggagtgat ctatcaggca ccagacttgg gatcagttat aaactctaga gtgcttactg 360
cagtgcatgg tattcagtca gcttttgatg aagctatgtc atactgtcga tatcatcctt 420
ccaaagggta ttggtggcac ttcaaagatc atgaagagca agataaagtc agacctaaag 480
ccaaaaggaa agaagaacca agctctattt ttcagagaca acgtgtggat gctttacttt 540
tagacctcag acaaaaattt ccacccaaat ttgtgcagct aaagcctgga gaaaagcctg 600
ttccagtgga tcaaacaaag aaagaggcag aacctatacc agaaactgta aaacctgagg 660
agaaggagac cacaaagaat gtacaacaga cagtgagtgc taaaggcccc cctgaaaaac 720
ggatgagact tcagtgagta ctggacaaaa gagaagcctg gaagactcct catgctagtt 780
atcatacctc agtactgtgg ctcttgagct ttgaagtact ttattgtaac cttcttattt 840
gtatggaatg cgcttatttt ttgaaaggat attaggccgg atgtggtggc tcacgcctgt 900
aatcccagca ctttgggagg ccatggcggg tggatcactt gaggtcagaa gttcaagacc 960
agcctgacca atatggtgaa accccgtctc tactaaaaat acaaaaatta gccgggcgtg 1020
gtggcgggcg cccatagtcc cagctactcg ggaggctgag acaggagact tgcttgaacc 1080
cgggaggtgg aggttgccct gagctgatta tcatgctgtt gcactccagc ttgggcgaca 1140
gaacgagact ttgtctcaaa aaaagaagaa aagatattat tcccatcatg atttcttgtg 1200
aatatttgtt atatgtcttc tggtaacctt tcctctcccg gacttgaagc aacctcacac 1260
actcacatgt ttactggtag atatgtttta aaagcaaaat aaaggtattt gtttttccaa 1320
aaaaaaaaaa aaaaaaaaaa aaaaaaaaac tcgag 1355

<210> 32
<211> 80
<212> PRT
<213> Homo sapien

<400> 32

Val	Ser	Arg	Ile	Arg	Gly	Gly	Ala	Lys	Lys	Arg	Lys	Lys	Lys	Ser	Tyr
1				5					10					15	
Thr	Thr	Pro	Lys	Lys	Asp	Lys	His	Gln	Arg	Lys	Lys	Val	Gln	Pro	Ala
			20					25				30			
Val	Leu	Lys	Tyr	Tyr	Lys	Val	Asp	Glu	Asn	Gly	Lys	Ile	Ser	Cys	Leu
		35					40					45			
Arg	Arg	Glu	Cys	Pro	Ser	Asp	Glu	Cys	Gly	Ala	Gly	Val	Phe	Met	Ala
	50					55					60				
Ser	His	Phe	Asp	Arg	His	Tyr	Cys	Gly	Lys	Cys	Cys	Leu	Thr	His	Cys
65					70					75					80

<210> 33
<211> 130
<212> PRT
<213> Homo sapien

<400> 33
Glu Ile Ser Asn Glu Val Arg Lys Phe Arg Thr Leu Thr Glu Leu Ile
1 5 10 15
Leu Asp Ala Gln Glu His Val Lys Asn Pro Tyr Lys Gly Lys Lys Leu
20 25 30
Lys Lys His Pro Asp Phe Pro Lys Lys Pro Leu Thr Pro Tyr Phe Arg
35 40 45
Phe Phe Met Glu Lys Arg Ala Lys Tyr Ala Lys Leu His Pro Gln Met
50 55 60
Ser Asn Leu Asp Leu Thr Lys Ile Leu Ser Lys Lys Tyr Lys Glu Leu
65 70 75 80
Pro Glu Lys Lys Lys Met Lys Tyr Val Pro Asp Phe Gln Arg Arg Glu
85 90 95
Thr Gly Val Arg Ala Lys Pro Gly Pro Ile Gln Gly Gly Ser Pro Pro
100 105 110
Pro Tyr Pro Glu Cys Gln Glu Ser Asp Ile Pro Glu Lys Pro Gln Asp
115 120 125
Pro Pro
130

<210> 34
<211> 506
<212> PRT
<213> Homo sapien

<400> 34
Asn Ser Glu Lys Glu Ile Pro Val Leu Asn Glu Leu Pro Val Pro Met
1 5 10 15
Val Ala Arg Tyr Ile Arg Ile Asn Pro Gln Ser Trp Phe Asp Asn Gly
20 25 30
Ser Ile Cys Met Arg Met Glu Ile Leu Gly Cys Pro Leu Pro Asp Pro
35 40 45
Asn Asn Tyr Tyr His Arg Arg Asn Glu Met Thr Thr Thr Asp Asp Leu
50 55 60
Asp Phe Lys His His Asn Tyr Lys Glu Met Arg Gln Leu Met Lys Val
65 70 75 80
Val Asn Glu Met Cys Pro Asn Ile Thr Arg Ile Tyr Asn Ile Gly Lys
85 90 95
Ser His Gln Gly Leu Lys Leu Tyr Ala Val Glu Ile Ser Asp His Pro
100 105 110
Gly Glu His Glu Val Gly Glu Pro Glu Phe His Tyr Ile Ala Gly Ala
115 120 125
His Gly Asn Glu Val Leu Gly Arg Glu Leu Leu Leu Leu Leu Leu His
130 135 140
Phe Leu Cys Gln Glu Tyr Ser Ala Gln Asn Ala Arg Ile Val Arg Leu
145 150 155 160
Val Glu Glu Thr Arg Ile His Ile Leu Pro Ser Leu Asn Pro Asp Gly
165 170 175
Tyr Glu Lys Ala Tyr Glu Gly Gly Ser Glu Leu Gly Gly Trp Ser Leu
180 185 190
Gly Arg Trp Thr His Asp Gly Ile Asp Ile Asn Asn Asn Phe Pro Asp
195 200 205
Leu Asn Ser Leu Leu Trp Glu Ala Glu Asp Gln Gln Asn Ala Pro Arg
210 215 220
Lys Val Pro Asn His Tyr Ile Ala Ile Pro Glu Trp Phe Leu Ser Glu
225 230 235 240
Asn Ala Thr Val Ala Thr Glu Thr Arg Ala Val Ile Ala Trp Met Glu

```
                245                 250                 255
Lys Ile Pro Phe Val Leu Gly Gly Asn Leu Gln Gly Gly Glu Leu Val
            260                 265                 270
Val Ala Tyr Pro Tyr Asp Met Val Arg Ser Leu Trp Lys Thr Gln Glu
        275                 280                 285
His Thr Pro Thr Pro Asp Asp His Val Phe Arg Trp Leu Ala Tyr Ser
    290                 295                 300
Tyr Ala Ser Thr His Arg Leu Met Thr Asp Ala Arg Arg Arg Val Cys
305                 310                 315                 320
His Thr Glu Asp Phe Gln Lys Glu Glu Gly Thr Val Asn Gly Ala Ser
                325                 330                 335
Trp His Thr Val Ala Gly Ser Leu Asn Asp Phe Ser Tyr Leu His Thr
            340                 345                 350
Asn Cys Phe Glu Leu Ser Ile Tyr Val Gly Cys Asp Lys Tyr Pro His
        355                 360                 365
Glu Ser Glu Leu Pro Glu Glu Trp Glu Asn Asn Arg Glu Ser Leu Ile
    370                 375                 380
Val Phe Met Glu Gln Val His Arg Gly Ile Lys Gly Ile Val Arg Asp
385                 390                 395                 400
Leu Gln Gly Lys Gly Ile Ser Asn Ala Val Ile Ser Val Glu Gly Val
                405                 410                 415
Asn His Asp Ile Arg Thr Ala Ser Asp Gly Asp Tyr Trp Arg Leu Leu
            420                 425                 430
Asn Pro Gly Glu Tyr Val Val Thr Ala Lys Ala Glu Gly Phe Ile Thr
        435                 440                 445
Ser Thr Lys Asn Cys Met Val Gly Tyr Asp Met Gly Ala Thr Arg Cys
    450                 455                 460
Asp Phe Thr Leu Thr Lys Thr Asn Leu Ala Arg Ile Arg Glu Ile Met
465                 470                 475                 480
Glu Thr Phe Gly Lys Gln Pro Val Ser Leu Pro Ser Arg Arg Leu Lys
                485                 490                 495
Leu Arg Gly Arg Lys Arg Arg Gln Arg Gly
            500                 505
```

<210> 35
<211> 96
<212> PRT
<213> Homo sapien

<400> 35

```
Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
 1               5                  10                  15
Arg Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
            20                  25                  30
Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Gln Phe Lys Thr
        35                  40                  45
Thr Gln Thr His Met Asp Arg Glu Lys Val Ala Leu Lys Asp Phe Ser
    50                  55                  60
Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65                  70                  75                  80
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Thr Gln Glu His Val
                85                  90                  95
```

<210> 36
<211> 129
<212> PRT
<213> Homo sapien

<400> 36

```
Gly Ile Val Val Phe Ser Leu Gly Ser Met Val Ser Glu Ile Pro Glu
 1               5                  10                  15
Lys Lys Ala Val Ala Ile Ala Asp Ala Leu Gly Lys Ile Pro Gln Thr
            20                  25                  30
Val Leu Trp Arg Tyr Thr Gly Thr Arg Pro Ser Asn Leu Ala Asn Asn
        35                  40                  45
Thr Ile Leu Val Gln Trp Leu Pro Gln Asn Asp Leu Leu Gly His Pro
    50                  55                  60
Met Thr Arg Ala Phe Ile Thr His Ala Ser Ser His Gly Val Asn Glu
65                  70                  75                  80
Ser Ile Cys Asn Gly Val Pro Met Val Met Ile Pro Leu Phe Gly Asp
                85                  90                  95
Gln Met Asp Asn Ala Lys Arg Arg Glu Thr Lys Gly Ala Gly Val Thr
            100                 105                 110
Leu Asn Val Leu Glu Met Thr Ser Glu Asp Leu Glu Asp Ala Leu Lys
        115                 120                 125
Ser
```

<210> 37
<211> 238
<212> PRT
<213> Homo sapien

<400> 37

```
Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu
 1               5                  10                  15
Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe
            20                  25                  30
Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr
        35                  40                  45
Leu Glu His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His
    50                  55                  60
Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser
65                  70                  75                  80
Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val
                85                  90                  95
Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu
            100                 105                 110
Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr
        115                 120                 125
Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His
    130                 135                 140
Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro
145                 150                 155                 160
Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu
                165                 170                 175
Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu Lys Pro Gly Glu Lys
            180                 185                 190
Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala Glu Pro Ile Pro Glu
        195                 200                 205
Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys Asn Val Gln Gln Thr
    210                 215                 220
Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met Arg Leu Gln
225                 230                 235
```

<210> 38

<211> 202
<212> PRT
<213> Homo sapien

<400> 38

```
Lys Gly Ser Glu Gly Glu Asn Pro Leu Thr Val Pro Gly Arg Glu Lys
 1               5                  10                  15
Glu Gly Met Leu Met Gly Val Lys Pro Gly Glu Asp Ala Ser Gly Pro
            20                  25                  30
Ala Glu Asp Leu Val Arg Arg Ser Glu Lys Asp Thr Ala Ala Val Val
        35                  40                  45
Ser Arg Gln Gly Ser Ser Leu Asn Leu Phe Glu Asp Val Gln Ile Thr
    50                  55                  60
Glu Pro Glu Ala Glu Pro Glu Ser Lys Ser Glu Pro Arg Pro Pro Ile
65                  70                  75                  80
Ser Ser Pro Arg Ala Pro Gln Thr Arg Ala Val Lys Pro Arg Leu His
                85                  90                  95
Pro Val Lys Pro Met Asn Ala Thr Ala Thr Lys Val Ala Asn Cys Ser
            100                 105                 110
Leu Gly Thr Ala Thr Ile Ile Gly Glu Asn Leu Asn Asn Glu Val Met
        115                 120                 125
Met Lys Lys Tyr Ser Pro Ser Asp Pro Ala Phe Ala Tyr Ala Gln Leu
    130                 135                 140
Thr His Asp Glu Leu Ile Gln Leu Val Leu Lys Gln Lys Glu Thr Ile
145                 150                 155                 160
Ser Lys Lys Glu Phe Gln Val Arg Glu Leu Glu Asp Tyr Ile Asp Asn
                165                 170                 175
Leu Leu Val Arg Val Met Glu Glu Thr Pro Asn Ile Leu Arg Ile Pro
            180                 185                 190
Thr Gln Val Gly Lys Lys Ala Gly Lys Met
        195                 200
```

<210> 39
<211> 243
<212> PRT
<213> Homo sapien

<400> 39

```
Val Asn Ala Leu Gly Ile Met Ala Ala Val Asp Ile Arg Asp Asn Leu
 1               5                  10                  15
Leu Gly Ile Ser Trp Val Asp Ser Ser Trp Ile Pro Ile Leu Asn Ser
            20                  25                  30
Gly Ser Val Leu Asp Tyr Phe Ser Glu Arg Ser Asn Pro Phe Tyr Asp
        35                  40                  45
Arg Thr Cys Asn Asn Glu Val Val Lys Met Gln Arg Leu Thr Leu Glu
    50                  55                  60
His Leu Asn Gln Met Val Gly Ile Glu Tyr Ile Leu Leu His Ala Gln
65                  70                  75                  80
Glu Pro Ile Leu Phe Ile Ile Arg Lys Gln Gln Arg Gln Ser Pro Ala
                85                  90                  95
Gln Val Ile Pro Leu Ala Asp Tyr Tyr Ile Ile Ala Gly Val Ile Tyr
            100                 105                 110
Gln Ala Pro Asp Leu Gly Ser Val Ile Asn Ser Arg Val Leu Thr Ala
        115                 120                 125
Val His Gly Ile Gln Ser Ala Phe Asp Glu Ala Met Ser Tyr Cys Arg
    130                 135                 140
Tyr His Pro Ser Lys Gly Tyr Trp Trp His Phe Lys Asp His Glu Glu
145                 150                 155                 160
```

```
Gln Asp Lys Val Arg Pro Lys Ala Lys Arg Lys Glu Glu Pro Ser Ser
                165                 170                 175
Ile Phe Gln Arg Gln Arg Val Asp Ala Leu Leu Leu Asp Leu Arg Gln
            180                 185                 190
Lys Ile Ser Thr Gln Ile Cys Ala Val Asp Gln Thr Lys Lys Glu Ala
        195                 200                 205
Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
    210                 215                 220
Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
225                 230                 235                 240
Arg Leu Gln
```

<210> 40
<211> 245
<212> PRT
<213> Homo sapien

<400> 40

```
Ala Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp
 1               5                  10                  15
Ser Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe
            20                  25                  30
Ser Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val
        35                  40                  45
Val Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly
    50                  55                  60
Ile Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile
65                  70                  75                  80
Arg Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp
                85                  90                  95
Tyr Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser
            100                 105                 110
Val Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala
        115                 120                 125
Phe Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr
    130                 135                 140
Trp Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys
145                 150                 155                 160
Ala Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val
                165                 170                 175
Asp Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val
            180                 185                 190
Gln Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys
        195                 200                 205
Glu Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr
    210                 215                 220
Thr Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys
225                 230                 235                 240
Arg Met Arg Leu Gln
                245
```

<210> 41
<211> 163
<212> PRT
<213> Homo sapien

<400> 41

```
Gly Glu Arg Gln Gly Leu Val Ala Arg Ala Arg Leu Ser Leu Arg Pro
 1               5                  10                  15
Ser Ile Pro Glu Leu Ser Glu Arg Thr Ser Arg Pro Cys Arg Ala Ser
            20                  25                  30
Pro Ala Ser Leu Pro Ser Gln His Thr Ser Ser Pro Ala Gln Ala Arg
        35                  40                  45
Val Arg Asn Leu Ala Gln Ser Thr Phe Pro Leu Ala Ala Gln Glu Thr
    50                  55                  60
Pro Gly Arg Ala Pro Ala His Ala Pro Leu Ser Ser Phe Val Pro Gly
65                  70                  75                  80
Val Gly Gly Arg Ser Pro Ala Ser Val Gly Ile Ser Ala Pro Gly Gly
                85                  90                  95
Gly Pro Ser Gly Ala Ala Ala Lys Ile Pro Leu Glu Leu Thr Gln Ser
            100                 105                 110
Arg Val Gln Lys Ile Trp Val Pro Val Asp His Arg Pro Ser Leu Pro
        115                 120                 125
Arg Ser Cys Gly Pro Lys Leu Thr Asn Ser Pro Ala Val Phe Val Met
    130                 135                 140
Val Gly Leu Pro Arg Pro Gly Gln Asp Leu Leu Leu His Glu Ser Leu
145                 150                 155                 160
Leu Ala Ala
```

<210> 42
<211> 243
<212> PRT
<213> Homo sapien

<400> 42

```
Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser Ser
 1               5                  10                  15
Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser Glu
            20                  25                  30
Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val Lys
        35                  40                  45
Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile Glu
    50                  55                  60
Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg Lys
65                  70                  75                  80
Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr Tyr
                85                  90                  95
Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val Ile
            100                 105                 110
Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe Asp
        115                 120                 125
Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp Trp
    130                 135                 140
His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala Lys
145                 150                 155                 160
Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp Ala
                165                 170                 175
Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln Leu
            180                 185                 190
Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu Ala
        195                 200                 205
Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr Lys
    210                 215                 220
Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg Met
```

225 230 235 240
Arg Leu Gln

<210> 43
<211> 244
<212> PRT
<213> Homo sapien

<400> 43
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser
1 5 10 15
Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser
20 25 30
Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val
35 40 45
Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile
50 55 60
Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg
65 70 75 80
Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr
85 90 95
Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val
100 105 110
Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe
115 120 125
Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp
130 135 140
Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala
145 150 155 160
Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp
165 170 175
Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln
180 185 190
Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu
195 200 205
Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr
210 215 220
Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg
225 230 235 240
Met Arg Leu Gln

<210> 44
<211> 109
<212> PRT
<213> Homo sapien

<400> 44
Glu Leu His Phe Ser Glu Phe Thr Ser Ala Val Ala Asp Met Lys Asn
1 5 10 15
Ser Val Ala Asp Arg Asp Asn Ser Pro Ser Ser Cys Ala Gly Leu Phe
20 25 30
Ile Ala Ser His Ile Gly Phe Asp Trp Pro Gly Val Trp Val His Leu
35 40 45
Asp Ile Ala Ala Pro Val His Ala Gly Glu Arg Ala Thr Gly Phe Gly
50 55 60
Val Ala Leu Leu Leu Ala Leu Phe Gly Arg Ala Ser Glu Asp Pro Leu

65 70 75 80
Leu Asn Leu Val Ser Pro Leu Asp Cys Glu Val Asp Ala Gln Glu Gly
85 90 95
Asp Asn Met Gly Arg Asp Ser Lys Arg Arg Arg Leu Val
100 105

<210> 45
<211> 324
<212> PRT
<213> Homo sapien

<400> 45
Arg Arg Pro Val Met Ala Gln Glu Thr Ala Pro Pro Cys Gly Pro Val
1 5 10 15
Ser Arg Gly Asp Ser Pro Ile Ile Glu Lys Met Glu Lys Arg Thr Cys
20 25 30
Ala Leu Cys Pro Glu Gly His Glu Trp Ser Gln Ile Tyr Phe Ser Pro
35 40 45
Ser Gly Asn Ile Val Ala His Glu Asn Cys Leu Leu Tyr Ser Ser Gly
50 55 60
Leu Val Glu Cys Glu Thr Leu Asp Leu Arg Asn Thr Ile Arg Asn Phe
65 70 75 80
Asp Val Lys Ser Val Lys Lys Glu Ile Trp Arg Gly Arg Arg Leu Lys
85 90 95
Cys Ser Phe Cys Asn Lys Gly Gly Ala Thr Val Gly Cys Asp Leu Trp
100 105 110
Phe Cys Lys Lys Ser Tyr His Tyr Val Cys Ala Lys Lys Asp Gln Ala
115 120 125
Ile Leu Gln Val Asp Gly Asn His Gly Thr Tyr Lys Leu Phe Cys Pro
130 135 140
Glu His Ser Pro Glu Gln Glu Glu Ala Thr Glu Ser Ala Asp Asp Pro
145 150 155 160
Ser Met Lys Lys Lys Arg Gly Lys Asn Lys Arg Leu Ser Ser Gly Pro
165 170 175
Pro Ala Gln Pro Lys Thr Met Lys Cys Ser Asn Ala Lys Arg His Met
180 185 190
Thr Glu Glu Pro His Gly His Thr Asp Ala Ala Val Lys Ser Pro Phe
195 200 205
Leu Lys Lys Cys Gln Glu Ala Gly Leu Leu Thr Glu Leu Phe Glu His
210 215 220
Ile Leu Glu Asn Met Asp Ser Val His Gly Arg Leu Val Asp Glu Thr
225 230 235 240
Ala Ser Glu Ser Asp Tyr Glu Gly Ile Glu Thr Leu Leu Phe Asp Cys
245 250 255
Gly Leu Phe Lys Asp Thr Leu Arg Lys Phe Gln Glu Val Ile Lys Ser
260 265 270
Lys Ala Cys Glu Trp Glu Glu Arg Gln Arg Gln Met Lys Gln Gln Leu
275 280 285
Glu Ala Leu Ala Asp Leu Gln Gln Ser Leu Cys Ser Phe Gln Glu Asn
290 295 300
Gly Asp Leu Asp Cys Ser Ser Ser Thr Ser Gly Ser Leu Leu Pro Pro
305 310 315 320
Glu Asp His Gln

<210> 46
<211> 244
<212> PRT

<213> Homo sapien

<400> 46

```
Ala Val Asp Ile Arg Asp Asn Leu Leu Gly Ile Ser Trp Val Asp Ser
 1               5                  10                  15
Ser Trp Ile Pro Ile Leu Asn Ser Gly Ser Val Leu Asp Tyr Phe Ser
            20                  25                  30
Glu Arg Ser Asn Pro Phe Tyr Asp Arg Thr Cys Asn Asn Glu Val Val
        35                  40                  45
Lys Met Gln Arg Leu Thr Leu Glu His Leu Asn Gln Met Val Gly Ile
    50                  55                  60
Glu Tyr Ile Leu Leu His Ala Gln Glu Pro Ile Leu Phe Ile Ile Arg
65                  70                  75                  80
Lys Gln Gln Arg Gln Ser Pro Ala Gln Val Ile Pro Leu Ala Asp Tyr
                85                  90                  95
Tyr Ile Ile Ala Gly Val Ile Tyr Gln Ala Pro Asp Leu Gly Ser Val
            100                 105                 110
Ile Asn Ser Arg Val Leu Thr Ala Val His Gly Ile Gln Ser Ala Phe
        115                 120                 125
Asp Glu Ala Met Ser Tyr Cys Arg Tyr His Pro Ser Lys Gly Tyr Trp
    130                 135                 140
Trp His Phe Lys Asp His Glu Glu Gln Asp Lys Val Arg Pro Lys Ala
145                 150                 155                 160
Lys Arg Lys Glu Glu Pro Ser Ser Ile Phe Gln Arg Gln Arg Val Asp
                165                 170                 175
Ala Leu Leu Leu Asp Leu Arg Gln Lys Phe Pro Pro Lys Phe Val Gln
            180                 185                 190
Leu Lys Pro Gly Glu Lys Pro Val Pro Val Asp Gln Thr Lys Lys Glu
        195                 200                 205
Ala Glu Pro Ile Pro Glu Thr Val Lys Pro Glu Glu Lys Glu Thr Thr
    210                 215                 220
Lys Asn Val Gln Gln Thr Val Ser Ala Lys Gly Pro Pro Glu Lys Arg
225                 230                 235                 240
Met Arg Leu Gln
```

<210> 47
<211> 14
<212> DNA
<213> Homo sapien

<400> 47
ttttttttt ttag 14

<210> 48
<211> 10
<212> DNA
<213> Homo sapien

<400> 48
cttcaacctc 10

<210> 49
<211> 496
<212> DNA
<213> Homo sapien

<400> 49

gcaccatgta ccgagcactt cggctcctcg cgcgctcgcg tcccctcgtg cgggctccag 60
ccgcagcctt agcttcggct cccggcttgg gtggcgcggc cgtgccctcg ttttggcctc 120
cgaacgcggc tcgaatggca agccaaaatt ccttccggat agaatatgat acctttggtg 180
aactaaaggt gccaaatgat aagtattatg gcgcccagac cgtgagatct acgatgaact 240
ttaagattgg aggtgtgaca gaacgcatgc caaccccagt tattaaagct tttggcatct 300
tgaagcgagc ggccgctgaa gtaaaccagg attatggtct tgatccaaag attgctaatg 360
caataatgaa ggcagcagat gaggtagctg aaggtaaatt aaatgatcat tttcctctcg 420
tggtatggca gactggatca ggaactcaga caaatatgaa tgtaaatgaa gtcattagcc 480
aatagagcaa ttgaaa 496

<210> 50
<211> 499
<212> DNA
<213> Homo sapien

<400> 50
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg 60
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240
ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggcg aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagt 499

<210> 51
<211> 887
<212> DNA
<213> Homo sapien

<400> 51
gagtctgagc agaaaggaaa agcagccttg gcagccacgt tagaggaata caaagccaca 60
gtggccagtg accagataga gatgaatcgc ctgaaggctc agctggagaa tgaaaagcag 120
aaagtggcag agctgtattc tatccataac tctggagaca aatctgatat tcaggacctc 180
ctggagagtg tcaggctgga caaagaaaaa gcagagactt tggctagtag cttgcaggaa 240
gatctggctc atacccgaaa tgatgccaat cgattacagg atgccattgc taaggtagag 300
gatgaatacc gagccttcca agaagaagct aagaaacaaa ttgaagattt gaatatgacg 360
ttagaaaaat taagatcaga cctggatgaa aaagaaacag aaaggagtga catgaaagaa 420
accatctttg aacttgaaga tgaagtagaa caacatcgtg ctgtgaaact tcatgacaac 480
ctcattattt ctgatctaga gaatacagtt aaaaaactcc aggaccaaaa gcacgacatg 540
gaaagagaaa taaagacact ccacagaaga cttcgggaag aatctgcgga atggcggcag 600
tttcaggctg atctccagac tgcagtagtc attgcaaatg acattaaatc tgaagcccaa 660
gaggagattg gtgatctaaa gcgccggtta catgaggctc aagaaaaaaa tgagaaactc 720
acaaaagaat tggaggaaat aaagtcacgc aagcaagagg aggagcgagg cgggtataca 780
attacatgaa tgccgttgag agagatttgg cagccttaag gcagggaatg ggactgagta 840
gaaggtcctc gacttcctca gagccaactc ctacagtaaa aaccctc 887

<210> 52
<211> 491
<212> DNA
<213> Homo sapien

<400> 52
ggcacgagct tttccaaaaa tcatgctgct cctttctcta aagttcttac attttataga 60
aaggaacctt tcactcttga ggcctactac agctctcctc aggatttgcc ctatccagat 120
cctgctatag ctcagttttc agttcagaaa gtcactcctc agtctgatgg ctccagttca 180
aaagtgaaag tcaaagttcg agtaaatgtc catggcattt tcagtgtgtc cagtgcatct 240

ttagtggagg ttcacaagtc tgaggaaaat gaggagccaa tggaaacaga tcagaatgca 300
aaggaggaag agaagatgca agtggaccag gaggaaccac atgttgaaga gcaacagcag 360
cagacaccag gcagaaaata aggcagagtc tgaagaaatg gagacctctc aagctggatc 420
caaggataaa aagatggacc aaccacccca agccaagaag gcaaaagtga agaccagtac 480
tgtggacctg g 491

<210> 53
<211> 787
<212> DNA
<213> Homo sapien

<400> 53
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
ccacaac 787

<210> 54
<211> 386
<212> DNA
<213> Homo sapien

<400> 54
ggcattttca gtgtgtccag tgcatcttta gtggaggttc acaagtctga ggaaaatgag 60
gagccaatgg aaacagatca gaatgcaaag gaggaagaga agatgcaagt ggaccaggag 120
gaaccacatg ttgaagagca acagcagcag acaccagcag aaaataaggc agagtctgaa 180
gaaatggaga cctctcaagc tggatccaag gataaaaaga tggaccaacc accccaagcc 240
aagaaggcaa aagtgaagac cagtactgtg gacctgccaa tcgagaatca gctattatgg 300
cagatagaca gagagatgct caacttgtac attgaaaatg agggtaagat gatcatgcag 360
gataaactgg agaaggagcg gaatga 386

<210> 55
<211> 1462
<212> DNA
<213> Homo sapien

<400> 55
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660

ggctcaataa tgcccaccac tgtggaggca gcctgatcaa taacatgtgg atcctgacag 720
cagctcactg cttcagaagc aactctaatc ctcgtgactg gattgccacg tctggtattt 780
ccacaacatt tcctaaacta agaatgagag taagaaatat tttaattcat aacaattata 840
aatctgcaac tcatgaaaat gacattgcac ttgtgagact tgagaacagt gtcaccttta 900
ccaaagatat ccatagtgtg tgtctcccag ctgctaccca gaatattcca cctggctcta 960
ctgcttatgt aacaggatgg ggcgctcaag aatatgctgg ccacacagtt ccagagctaa 1020
ggcaaggaca ggtcagaata ataagtaatg atgtatgtaa tgcaccacat agttataatg 1080
gagccatctt gtctggaatg ctgtgtgctg gagtacctca aggtggagtg gacgcatgtc 1140
agggtgactc tggtggccca ctagtacaag aagactcacg gcggctttgg tttattgtgg 1200
ggatagtaag ctggggagat cagtgtggcc tgccggataa gccaggagtg tatactcgag 1260
tgacagcata cattgactgg attaggcaac aaactgggat ctagtgcaac aagtgcatcc 1320
ctgttgcaaa gtctgtatgc aggtgtgcct gtcttaaatt ccaaagcttt acatttcaac 1380
tgaaaaagaa actagaaatg tcctaattta acatcttgtt acataaatat ggtttaacaa 1440
aaaaaaaaaa aaaaaactcg ag 1462

<210> 56
<211> 159
<212> PRT
<213> Homo sapien

<400> 56

```
Thr Met Tyr Arg Ala Leu Arg Leu Leu Ala Arg Ser Arg Pro Leu Val
 1               5                  10                  15
Arg Ala Pro Ala Ala Ala Leu Ala Ser Ala Pro Gly Leu Gly Gly Ala
            20                  25                  30
Ala Val Pro Ser Phe Trp Pro Pro Asn Ala Ala Arg Met Ala Ser Gln
        35                  40                  45
Asn Ser Phe Arg Ile Glu Tyr Asp Thr Phe Gly Glu Leu Lys Val Pro
    50                  55                  60
Asn Asp Lys Tyr Tyr Gly Ala Gln Thr Val Arg Ser Thr Met Asn Phe
65                  70                  75                  80
Lys Ile Gly Gly Val Thr Glu Arg Met Pro Thr Pro Val Ile Lys Ala
                85                  90                  95
Phe Gly Ile Leu Lys Arg Ala Ala Ala Glu Val Asn Gln Asp Tyr Gly
            100                 105                 110
Leu Asp Pro Lys Ile Ala Asn Ala Ile Met Lys Ala Ala Asp Glu Val
        115                 120                 125
Ala Glu Gly Lys Leu Asn Asp His Phe Pro Leu Val Val Trp Gln Thr
    130                 135                 140
Gly Ser Gly Thr Gln Thr Asn Met Asn Val Asn Glu Val Ile Ser
145                 150                 155
```

<210> 57
<211> 165
<212> PRT
<213> Homo sapien

<400> 57

```
Lys Lys Ser Met Phe Ala Glu Ile Gln Ile Gln Asp Lys Asp Arg Met
 1               5                  10                  15
Gly Thr Ala Gly Lys Val Ile Lys Cys Lys Ala Ala Val Leu Trp Glu
            20                  25                  30
Gln Lys Gln Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys
        35                  40                  45
Thr Lys Glu Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr
    50                  55                  60
Asp Asp His Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile
65                  70                  75                  80
```

```
Val Gly His Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val
                85                  90                  95
Thr Thr Val Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln
            100                 105                 110
Cys Arg Glu Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile
        115                 120                 125
Arg Ser Asp Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg
    130                 135                 140
Phe Thr Cys Lys Gly Glu Pro Val His His Phe Met Asn Thr Ser Thr
145                 150                 155                 160
Phe Thr Glu Tyr Thr
                165
```

<210> 58
<211> 259
<212> PRT
<213> Homo sapien

<400> 58

```
Glu Ser Glu Gln Lys Gly Lys Ala Ala Leu Ala Ala Thr Leu Glu Glu
 1               5                  10                  15
Tyr Lys Ala Thr Val Ala Ser Asp Gln Ile Glu Met Asn Arg Leu Lys
            20                  25                  30
Ala Gln Leu Glu Asn Glu Lys Gln Lys Val Ala Glu Leu Tyr Ser Ile
        35                  40                  45
His Asn Ser Gly Asp Lys Ser Asp Ile Gln Asp Leu Leu Glu Ser Val
    50                  55                  60
Arg Leu Asp Lys Glu Lys Ala Glu Thr Leu Ala Ser Ser Leu Gln Glu
65                  70                  75                  80
Asp Leu Ala His Thr Arg Asn Asp Ala Asn Arg Leu Gln Asp Ala Ile
                85                  90                  95
Ala Lys Val Glu Asp Glu Tyr Arg Ala Phe Gln Glu Glu Ala Lys Lys
            100                 105                 110
Gln Ile Glu Asp Leu Asn Met Thr Leu Glu Lys Leu Arg Ser Asp Leu
        115                 120                 125
Asp Glu Lys Glu Thr Glu Arg Ser Asp Met Lys Glu Thr Ile Phe Glu
    130                 135                 140
Leu Glu Asp Glu Val Glu Gln His Arg Ala Val Lys Leu His Asp Asn
145                 150                 155                 160
Leu Ile Ile Ser Asp Leu Glu Asn Thr Val Lys Lys Leu Gln Asp Gln
                165                 170                 175
Lys His Asp Met Glu Arg Glu Ile Lys Thr Leu His Arg Arg Leu Arg
            180                 185                 190
Glu Glu Ser Ala Glu Trp Arg Gln Phe Gln Ala Asp Leu Gln Thr Ala
        195                 200                 205
Val Val Ile Ala Asn Asp Ile Lys Ser Glu Ala Gln Glu Glu Ile Gly
    210                 215                 220
Asp Leu Lys Arg Arg Leu His Glu Ala Gln Glu Lys Asn Glu Lys Leu
225                 230                 235                 240
Thr Lys Glu Leu Glu Glu Ile Lys Ser Arg Lys Gln Glu Glu Glu Arg
                245                 250                 255
Gly Gly Tyr
```

<210> 59
<211> 125
<212> PRT
<213> Homo sapien

<400> 59

```
Gly Thr Ser Phe Ser Lys Asn His Ala Ala Pro Phe Ser Lys Val Leu
 1               5                  10                  15
Thr Phe Tyr Arg Lys Glu Pro Phe Thr Leu Glu Ala Tyr Tyr Ser Ser
            20                  25                  30
Pro Gln Asp Leu Pro Tyr Pro Asp Pro Ala Ile Ala Gln Phe Ser Val
        35                  40                  45
Gln Lys Val Thr Pro Gln Ser Asp Gly Ser Ser Ser Lys Val Lys Val
    50                  55                  60
Lys Val Arg Val Asn Val His Gly Ile Phe Ser Val Ser Ser Ala Ser
65                  70                  75                  80
Leu Val Glu Val His Lys Ser Glu Glu Asn Glu Glu Pro Met Glu Thr
                85                  90                  95
Asp Gln Asn Ala Lys Glu Glu Glu Lys Met Gln Val Asp Gln Glu Glu
            100                 105                 110
Pro His Val Glu Glu Gln Gln Gln Gln Thr Pro Gly Arg
        115                 120                 125
```

<210> 60
<211> 246
<212> PRT
<213> Homo sapien

<400> 60

```
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
 1               5                  10                  15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr
                245
```

<210> 61
<211> 128
<212> PRT
<213> Homo sapien

<400> 61

```
Gly Ile Phe Ser Val Ser Ser Ala Ser Leu Val Glu Val His Lys Ser
 1               5                  10                  15
Glu Glu Asn Glu Glu Pro Met Glu Thr Asp Gln Asn Ala Lys Glu Glu
            20                  25                  30
Glu Lys Met Gln Val Asp Gln Glu Glu Pro His Val Glu Glu Gln Gln
        35                  40                  45
Gln Gln Thr Pro Ala Glu Asn Lys Ala Glu Ser Glu Glu Met Glu Thr
    50                  55                  60
Ser Gln Ala Gly Ser Lys Asp Lys Lys Met Asp Gln Pro Pro Gln Ala
65                  70                  75                  80
Lys Lys Ala Lys Val Lys Thr Ser Thr Val Asp Leu Pro Ile Glu Asn
                85                  90                  95
Gln Leu Leu Trp Gln Ile Asp Arg Glu Met Leu Asn Leu Tyr Ile Glu
            100                 105                 110
Asn Glu Gly Lys Met Ile Met Gln Asp Lys Leu Glu Lys Glu Arg Asn
        115                 120                 125
```

<210> 62
<211> 418
<212> PRT
<213> Homo sapien

<400> 62

```
Met Tyr Arg Pro Ala Arg Val Thr Ser Thr Ser Arg Phe Leu Asn Pro
 1               5                  10                  15
Tyr Val Val Cys Phe Ile Val Val Ala Gly Val Val Ile Leu Ala Val
            20                  25                  30
Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
```

```
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Ile Asp Trp Ile Arg Gln Gln Thr
                405                 410                 415
Gly Ile
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<210> 63
<211> 776
<212> DNA
<213> Homo sapien

<400> 63

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cacagatggt gatagaggaa tccatcttgc agtcagataa agccctcact gatagagaga      60
aggcagtagc agtggatcgg gccaagaagg aggcagctga gaaggaacag gaacttttaa     120
aacagaaatt acaggagcag ccagcaacag atggaggctc aagataagag tcgcaaggaa     180
aactagccaa ctgaaggaga agctgcagat ggagagagaa cacctactga gagagcagat     240
tatgatgttg gagcacacgc agaaggtcca aaatgattgg cttcatgaag gatttaagaa     300
gaagtatgag gagatgaatg cagagataag tcaatttaaa cgtatgattg atactacaaa     360
aaatgatgat actccctgga ttgcacgaac cttggacaac cttgccgatg agctaactgc     420
aatattgtct gctcctgcta aattaattgg tcatggtgtc aaaggtgtga gctcactctt     480
taaaaagcat aagctcccct tttaaggata ttatagattg tacatatatg ctttggacta     540
tttttgatct gtatgttttt cattttcatt cagcaagttt ttttttttt tcagagtctt     600
actctgttgc ccaggctgga gtacagtggt gcaatctcag ctcactgcaa cctctgcctc     660
ctgggttcaa gagattcacc tgcctcagcc ccctagtagc tgggattata ggtgtacacc     720
accacaccca gctaattttt gtatttttag tagagatggg gtttcactat gttggc         776
```

<210> 64
<211> 160
<212> DNA
<213> Homo sapien

<400> 64

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gcagcgctct cggttgcagt acccactgga aggacttagg cgctcgcgtg gacaccgcaa      60
gcccctcagt agcctcggcc caagaggcct gctttccact cgctagcccc gccgggggtc     120
cgtgtcctgt ctcggtggcc ggacccgggc ccgagcccga                           160
```

<210> 65
<211> 72

<212> PRT
<213> Homo sapien

<400> 65

```
Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser Ser Ile
 1               5                  10                  15
Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly Gly Val
            20                  25                  30
Ala Ser Gly Ser Leu Val Ala Thr Leu Gln Ser Leu Gly Ala Thr Gly
        35                  40                  45
Leu Ser Gly Leu Thr Lys Phe Ile Leu Gly Ser Ile Gly Ser Ala Ile
    50                  55                  60
Ala Ala Val Ile Ala Arg Phe Tyr
65                  70
```

<210> 66
<211> 2581
<212> DNA
<213> Homo sapien

<400> 66

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ctttcaaccc gcgctcgccg gctccagccc cgcgcgcccc cacccttgc cctcccggcg      60
gctccgcagg gtgaggtggc tttgaccccg ggttgcccgg ccagcacgac cgaggaggtg     120
gctggacagc tggaggatga acggagaagc cgactgcccc acagacctgg aaatggccgc     180
ccccaaaggc caagaccgtt ggtcccagga agacatgctg actttgctgg aatgcatgaa     240
gaacaacctt ccatccaatg acagctccaa gttcaaaacc accgaatcac acatggactg     300
ggaaaaagta gcatttaaag acttttctgg agacatgtgc aagctcaaat gggtggagat     360
ttctaatgag gtgaggaagt tccgtacatt gacagaattg atcctcgatg ctcaggaaca     420
tgttaaaaat ccttacaaag gcaaaaaact caagaaacac ccagacttcc caaagaagcc     480
cctgacccct tatttccgct tcttcatgga gaagcgggcc aagtatgcga aactccaccc     540
tgagatgagc aacctggacc taaccaagat tctgtccaag aaatacaagg agcttccgga     600
gaagaagaag atgaaatata ttcaggactt ccagagagag aaacaggagt tcgagcgaaa     660
cctggcccga ttcagggagg atcaccccga cctaatccag aatgccaaga aatcggacat     720
cccagagaag cccaaaaccc cccagcagct gtggtacacc cacgagaaga aggtgtatct     780
caaagtgcgg ccagatgcca ctacgaagga ggtgaaggac tccctgggga agcagtggtc     840
tcagctctcg gacaaaaaga ggctgaaatg gattcataag gccctggagc agcggaagga     900
gtacgaggag atcatgagag actatatcca gaagcaccca gagctgaaca tcagtgagga     960
gggtatcacc aagtccaccc tcaccaaggc cgaacgccag ctcaaggaca agtttgacgg    1020
gcgacccacc aagccacctc cgaacagcta ctcgctgtac tgcgcagagc tcatggccaa    1080
catgaaggac gtgcccagca cagagcgcat ggtgctgtgc agccagcagt ggaagctgct    1140
gtcccagaag gagaaggacg cctatcacaa gaagtgtgat cagaaaaaga aagattacga    1200
ggtggagctg ctccgtttcc tcgagagcct gcctgaggag gagcagcagc gggtcttggg    1260
ggaagagaag atgctgaaca tcaacaagaa gcaggccacc agccccgcct ccaagaagcc    1320
agcccaggaa gggggcaagg gcggctccga gaagcccaag cggcccgtgt cggccatgtt    1380
catcttctcg gaggagaaac ggcggcagct gcaggaggag cggcctgagc tctccgagag    1440
cgagctgacc cgcctgctgg cccgaatgtg gaacgacctg tctgagaaga agaaggccaa    1500
gtacaaggcc cgagaggcgg cgctcaaggc tcagtcggag aggaagcccg gcggggagcg    1560
cgaggaacgg ggcaagctgc ccgagtcccc caaaagagct gaggagatct ggcaacagag    1620
cgttatcggc gactacctgg cccgcttcaa gaatgaccgg gtgaaggcct tgaaagccat    1680
ggaaatgacc tggaataaca tggaaaagaa ggagaaactg atgtggatta agaaggcagc    1740
cgaagaccaa aagcgatatg agagagagct gagtgagatg cgggcacctc cagctgctac    1800
aaattcttcc aagaagatga aattccaggg agaacccaag aagcctccca tgaacggtta    1860
ccagaagttc tcccaggagc tgctgtccaa tggggagctg aaccacctgc cgctgaagga    1920
gcgcatggtg gagatcggca gtcgctggca gcgcatctcc cagagccaga aggagcacta    1980
caaaaagctg gccgaggagc agcaaaagca gtacaaggtg cacctggacc tctgggttaa    2040
gagcctgtct ccccaggacc gtgcagcata taaagagtac atctccaata aacgtaagag    2100
catgaccaag ctgcgaggcc caaaccccaa atccagccgg actactctgc agtccaagtc    2160
ggagtccgag gaggatgatg aagaggatga ggatgacgag gacgaggatg aagaagagga    2220
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agatgatgag aatggggact cctctgaaga tggcggcgac tcctctgagt ccagcagcga 2280
ggacgagagc gaggatgggg atgagaatga agaggatgac gaggacgaag acgacgacga 2340
ggatgacgat gaggatgaag ataatgagtc cgagggcagc agctccagct cctcctcctt 2400
aggggactcc tcagactttg actccaactg aggcttagcc ccaccccagg ggagccaggg 2460
agagcccagg agctcccctc cccaactgac caccttttgtt tcttccccat gttctgtccc 2520
ttgcccccct ggcctccccc actttctttc tttctttaaa aaaaaaaaaa aaaaactcga 2580
g 2581

<210> 67
<211> 764
<212> PRT
<213> Homo sapien

<400> 67

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Met Asn Gly Glu Ala Asp Cys Pro Thr Asp Leu Glu Met Ala Ala Pro
 1               5                  10                  15
Lys Gly Gln Asp Arg Trp Ser Gln Glu Asp Met Leu Thr Leu Leu Glu
            20                  25                  30
Cys Met Lys Asn Asn Leu Pro Ser Asn Asp Ser Ser Lys Phe Lys Thr
        35                  40                  45
Thr Glu Ser His Met Asp Trp Glu Lys Val Ala Phe Lys Asp Phe Ser
    50                  55                  60
Gly Asp Met Cys Lys Leu Lys Trp Val Glu Ile Ser Asn Glu Val Arg
65                  70                  75                  80
Lys Phe Arg Thr Leu Thr Glu Leu Ile Leu Asp Ala Gln Glu His Val
                85                  90                  95
Lys Asn Pro Tyr Lys Gly Lys Lys Leu Lys Lys His Pro Asp Phe Pro
            100                 105                 110
Lys Lys Pro Leu Thr Pro Tyr Phe Arg Phe Phe Met Glu Lys Arg Ala
        115                 120                 125
Lys Tyr Ala Lys Leu His Pro Glu Met Ser Asn Leu Asp Leu Thr Lys
    130                 135                 140
Ile Leu Ser Lys Lys Tyr Lys Glu Leu Pro Glu Lys Lys Lys Met Lys
145                 150                 155                 160
Tyr Ile Gln Asp Phe Gln Arg Glu Lys Gln Glu Phe Glu Arg Asn Leu
                165                 170                 175
Ala Arg Phe Arg Glu Asp His Pro Asp Leu Ile Gln Asn Ala Lys Lys
            180                 185                 190
Ser Asp Ile Pro Glu Lys Pro Lys Thr Pro Gln Gln Leu Trp Tyr Thr
        195                 200                 205
His Glu Lys Lys Val Tyr Leu Lys Val Arg Pro Asp Ala Thr Thr Lys
    210                 215                 220
Glu Val Lys Asp Ser Leu Gly Lys Gln Trp Ser Gln Leu Ser Asp Lys
225                 230                 235                 240
Lys Arg Leu Lys Trp Ile His Lys Ala Leu Glu Gln Arg Lys Glu Tyr
                245                 250                 255
Glu Glu Ile Met Arg Asp Tyr Ile Gln Lys His Pro Glu Leu Asn Ile
            260                 265                 270
Ser Glu Glu Gly Ile Thr Lys Ser Thr Leu Thr Lys Ala Glu Arg Gln
        275                 280                 285
Leu Lys Asp Lys Phe Asp Gly Arg Pro Thr Lys Pro Pro Pro Asn Ser
    290                 295                 300
Tyr Ser Leu Tyr Cys Ala Glu Leu Met Ala Asn Met Lys Asp Val Pro
305                 310                 315                 320
Ser Thr Glu Arg Met Val Leu Cys Ser Gln Gln Trp Lys Leu Leu Ser
                325                 330                 335
Gln Lys Glu Lys Asp Ala Tyr His Lys Lys Cys Asp Gln Lys Lys Lys
            340                 345                 350
```

```
Asp Tyr Glu Val Glu Leu Leu Arg Phe Leu Glu Ser Leu Pro Glu Glu
        355                 360                 365
Glu Gln Gln Arg Val Leu Gly Glu Glu Lys Met Leu Asn Ile Asn Lys
    370                 375                 380
Lys Gln Ala Thr Ser Pro Ala Ser Lys Lys Pro Ala Gln Glu Gly Gly
385                 390                 395                 400
Lys Gly Gly Ser Glu Lys Pro Lys Arg Pro Val Ser Ala Met Phe Ile
                405                 410                 415
Phe Ser Glu Glu Lys Arg Arg Gln Leu Gln Glu Glu Arg Pro Glu Leu
            420                 425                 430
Ser Glu Ser Glu Leu Thr Arg Leu Leu Ala Arg Met Trp Asn Asp Leu
        435                 440                 445
Ser Glu Lys Lys Lys Ala Lys Tyr Lys Ala Arg Glu Ala Ala Leu Lys
    450                 455                 460
Ala Gln Ser Glu Arg Lys Pro Gly Gly Glu Arg Glu Glu Arg Gly Lys
465                 470                 475                 480
Leu Pro Glu Ser Pro Lys Arg Ala Glu Glu Ile Trp Gln Gln Ser Val
                485                 490                 495
Ile Gly Asp Tyr Leu Ala Arg Phe Lys Asn Asp Arg Val Lys Ala Leu
            500                 505                 510
Lys Ala Met Glu Met Thr Trp Asn Asn Met Glu Lys Lys Glu Lys Leu
        515                 520                 525
Met Trp Ile Lys Lys Ala Ala Glu Asp Gln Lys Arg Tyr Glu Arg Glu
    530                 535                 540
Leu Ser Glu Met Arg Ala Pro Pro Ala Ala Thr Asn Ser Ser Lys Lys
545                 550                 555                 560
Met Lys Phe Gln Gly Glu Pro Lys Lys Pro Pro Met Asn Gly Tyr Gln
                565                 570                 575
Lys Phe Ser Gln Glu Leu Leu Ser Asn Gly Glu Leu Asn His Leu Pro
            580                 585                 590
Leu Lys Glu Arg Met Val Glu Ile Gly Ser Arg Trp Gln Arg Ile Ser
        595                 600                 605
Gln Ser Gln Lys Glu His Tyr Lys Lys Leu Ala Glu Glu Gln Gln Lys
    610                 615                 620
Gln Tyr Lys Val His Leu Asp Leu Trp Val Lys Ser Leu Ser Pro Gln
625                 630                 635                 640
Asp Arg Ala Ala Tyr Lys Glu Tyr Ile Ser Asn Lys Arg Lys Ser Met
                645                 650                 655
Thr Lys Leu Arg Gly Pro Asn Pro Lys Ser Ser Arg Thr Thr Leu Gln
            660                 665                 670
Ser Lys Ser Glu Ser Glu Glu Asp Asp Glu Glu Asp Glu Asp Asp Glu
        675                 680                 685
Asp Glu Asp Glu Glu Glu Glu Asp Asp Glu Asn Gly Asp Ser Ser Glu
    690                 695                 700
Asp Gly Gly Asp Ser Ser Glu Ser Ser Ser Glu Asp Glu Ser Glu Asp
705                 710                 715                 720
Gly Asp Glu Asn Glu Glu Asp Asp Glu Asp Glu Asp Asp Asp Glu Asp
                725                 730                 735
Asp Asp Glu Asp Glu Asp Asn Glu Ser Glu Gly Ser Ser Ser Ser Ser
            740                 745                 750
Ser Ser Leu Gly Asp Ser Ser Asp Phe Asp Ser Asn
        755                 760
```

<210> 68
<211> 434
<212> DNA
<213> Homo sapien

<400> 68
ctaagatgct ggatgctgaa gacatcgtcg gaactgcccg gccagatgag aaagccatta 60
tgacttatgt gtctagcttc tatcatgcct tctctggagc ccagaaggca gaaacagcag 120
ccaatcgcat ctgcaaagtg ttggcggtca atcaagagaa cgagcagctt atggaagact 180
atgagaagct ggccagtgat ctgttggagt ggatccgccg caccatccca tggctggaga 240
atcgggtgcc tgagaacacc atgcatgcca tgcagcagaa gctggaggac ttccgagact 300
atagacgcct gcacaagccg cccaaggtgc aggagaagtg ccagctggag atcaacttta 360
acacgctgca gaccaaactg cggctcagca accggcctgc cttcatgccc tccgagggca 420
ggatggtctc ggat 434

<210> 69
<211> 244
<212> DNA
<213> Homo sapien

<400> 69
aggcagcatg ctcgttgaga gtcatcacca ctccctaatc tcaagtacgc agggacacaa 60
acactgcgga aggccgcagg gtcctctgcc taggaaaacc agagaccttt gttcacttgt 120
ttatgtgctg accttccctc cactattgtc ctgtgaccct gccaaatccc cctttgtgag 180
aaacacccaa gaatgatcaa taaaaaataa attaatttag gaaaaaaaaa aaaaaaaact 240
cgag 244

<210> 70
<211> 437
<212> DNA
<213> Homo sapien

<400> 70
ctgggacggg agcgtccagc gggactcgaa ccccagatgt gaaggcgttt ctggaaagtc 60
cttggtccct ggatccagcg tcggccagcc cagagcccgt gccgcacatc cttgcgtcct 120
ccaggcagtg ggaccccgcg agctgcacgt ccctgggcac ggacaagtgt gaggcactgt 180
tggggctgtg ccaggtgcgg ggtgggctgc ccccttctc agaaccttcc agcctggtgc 240
cgtggccccc aggccggagt cttcctaagg ctgtgaggcc acccctgtcc tggcctccgt 300
tctcgcagca gcagaccttg cccgtgatga gcggggaggc ccttggctgg ctgggccagg 360
ctggttccct ggccatgggg gctgcacctc tgggggagcc agccaaggag gaccccatgc 420
tggcgcagga agccggg 437

<210> 71
<211> 271
<212> DNA
<213> Homo sapien

<400> 71
gcgcagagtt ctgtcgtcca ccatcgagtg aggaagagag cattggttcc cctgagatag 60
aagagatggc tctcttcagt gcccagtctc catacattaa cccgatcatc ccctttactg 120
gaccaatcca aggagggctg caggagggac ttcaggtgac cctccagggg actaccgaga 180
gttttgcaca aaagtttgtg gtgaactttt cagaacagct tcaatggaga tgacttggcc 240
ttccacttca accccggtta tgaggaagga g 271

<210> 72
<211> 290
<212> DNA
<213> Homo sapien

<400> 72
ccgagcccta cccggaggtc tccagaatcc ccaccgtcag gggatgcaac ggctccctgt 60
ctggtgccct ctcctgctgc gaggactcgg cccagggctc gggcccgccc aaggccccta 120
cggtggccga gggtcccagc tcctgccttc ggcggaacgt gatcagcgag agggagcgca 180

ggaagcggat gtcgttgagc tgtgagcgtc tgcgggccct gctgccccag ttcgatggcc 240
ggcgggagga catggcctcg gtcctggaga tgtctgttgc aattcctgcg 290

<210> 73
<211> 144
<212> PRT
<213> Homo sapien

<400> 73
Lys Met Leu Asp Ala Glu Asp Ile Val Gly Thr Ala Arg Pro Asp Glu
1 5 10 15
Lys Ala Ile Met Thr Tyr Val Ser Ser Phe Tyr His Ala Phe Ser Gly
20 25 30
Ala Gln Lys Ala Glu Thr Ala Ala Asn Arg Ile Cys Lys Val Leu Ala
35 40 45
Val Asn Gln Glu Asn Glu Gln Leu Met Glu Asp Tyr Glu Lys Leu Ala
50 55 60
Ser Asp Leu Leu Glu Trp Ile Arg Arg Thr Ile Pro Trp Leu Glu Asn
65 70 75 80
Arg Val Pro Glu Asn Thr Met His Ala Met Gln Gln Lys Leu Glu Asp
85 90 95
Phe Arg Asp Tyr Arg Arg Leu His Lys Pro Pro Lys Val Gln Glu Lys
100 105 110
Cys Gln Leu Glu Ile Asn Phe Asn Thr Leu Gln Thr Lys Leu Arg Leu
115 120 125
Ser Asn Arg Pro Ala Phe Met Pro Ser Glu Gly Arg Met Val Ser Asp
130 135 140

<210> 74
<211> 64
<212> PRT
<213> Homo sapien

<400> 74
Gly Ser Met Leu Val Glu Ser His His His Ser Leu Ile Ser Ser Thr
1 5 10 15
Gln Gly His Lys His Cys Gly Arg Pro Gln Gly Pro Leu Pro Arg Lys
20 25 30
Thr Arg Asp Leu Cys Ser Leu Val Tyr Val Leu Thr Phe Pro Pro Leu
35 40 45
Leu Ser Cys Asp Pro Ala Lys Ser Pro Phe Val Arg Asn Thr Gln Glu
50 55 60

<210> 75
<211> 145
<212> PRT
<213> Homo sapien

<400> 75
Gly Thr Gly Ala Ser Ser Gly Thr Arg Thr Pro Asp Val Lys Ala Phe
1 5 10 15
Leu Glu Ser Pro Trp Ser Leu Asp Pro Ala Ser Ala Ser Pro Glu Pro
20 25 30
Val Pro His Ile Leu Ala Ser Ser Arg Gln Trp Asp Pro Ala Ser Cys
35 40 45
Thr Ser Leu Gly Thr Asp Lys Cys Glu Ala Leu Leu Gly Leu Cys Gln
50 55 60
Val Arg Gly Gly Leu Pro Pro Phe Ser Glu Pro Ser Ser Leu Val Pro

65 70 75 80
Trp Pro Pro Gly Arg Ser Leu Pro Lys Ala Val Arg Pro Pro Leu Ser
85 90 95
Trp Pro Pro Phe Ser Gln Gln Gln Thr Leu Pro Val Met Ser Gly Glu
100 105 110
Ala Leu Gly Trp Leu Gly Gln Ala Gly Ser Leu Ala Met Gly Ala Ala
115 120 125
Pro Leu Gly Glu Pro Ala Lys Glu Asp Pro Met Leu Ala Gln Glu Ala
130 135 140
Gly
145

<210> 76
<211> 69
<212> PRT
<213> Homo sapien

<400> 76
Ala Glu Phe Cys Arg Pro Pro Ser Ser Glu Glu Glu Ser Ile Gly Ser
1 5 10 15
Pro Glu Ile Glu Glu Met Ala Leu Phe Ser Ala Gln Ser Pro Tyr Ile
20 25 30
Asn Pro Ile Ile Pro Phe Thr Gly Pro Ile Gln Gly Gly Leu Gln Glu
35 40 45
Gly Leu Gln Val Thr Leu Gln Gly Thr Thr Glu Ser Phe Ala Gln Lys
50 55 60
Phe Val Val Asn Phe
65

<210> 77
<211> 96
<212> PRT
<213> Homo sapien

<400> 77
Glu Pro Tyr Pro Glu Val Ser Arg Ile Pro Thr Val Arg Gly Cys Asn
1 5 10 15
Gly Ser Leu Ser Gly Ala Leu Ser Cys Cys Glu Asp Ser Ala Gln Gly
20 25 30
Ser Gly Pro Pro Lys Ala Pro Thr Val Ala Glu Gly Pro Ser Ser Cys
35 40 45
Leu Arg Arg Asn Val Ile Ser Glu Arg Glu Arg Arg Lys Arg Met Ser
50 55 60
Leu Ser Cys Glu Arg Leu Arg Ala Leu Leu Pro Gln Phe Asp Gly Arg
65 70 75 80
Arg Glu Asp Met Ala Ser Val Leu Glu Met Ser Val Ala Ile Pro Ala
85 90 95

<210> 78
<211> 2076
<212> DNA
<213> Homo sapien

<400> 78
agaaaaagtc tatgtttgca gaaatacaga tccaagacaa agacaggatg ggcactgctg 60
gaaaagttat taaatgcaaa gcagctgtgc tttgggagca gaagcaaccc ttctccattg 120
aggaaataga agttgcccca ccaaagacta aagaagttcg cattaagatt ttggccacag 180
gaatctgtcg cacagatgac catgtgataa aaggaacaat ggtgtccaag tttccagtga 240

ttgtgggaca tgaggcaact gggattgtag agagcattgg agaaggagtg actacagtga 300
aaccaggtga caaagtcatc cctctctttc tgccacaatg tagagaatgc aatgcttgtc 360
gcaacccaga tggcaacctt tgcattagga gcgatattac tggtcgtgga gtactggctg 420
atggcaccac cagatttaca tgcaagggca aaccagtcca ccacttcatg aacaccagta 480
catttaccga gtacacagtg gtggatgaat cttctgttgc taagattgat gatgcagctc 540
ctcctgagaa agtctgttta attggctgtg ggttttccac tggatatggc gctgctgtta 600
aaactggcaa ggtcaaacct ggttccactt gcgtcgtctt tggcctgaga ggagttggcc 660
tgtcagtcat catgggctgt aagtcagctg gtgcatctag gatcattggg attgacctca 720
acaaagacaa atttgagaag gccatggctg taggtgccac tgagtgtatc agtcccaagg 780
actctaccaa acccatcagt gaggtgctgt cagaaatgac aggcaacaac gtgggataca 840
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actatgggac cagcgtggtt gtaggagttc ctccatcagc caagatgctc acctatgacc 960
cgatgttgct cttcactgga cgcacatgga agggatgtgt ctttggaggt ttgaaaagca 1020
gagatgatgt cccaaaacta gtgactgagt tcctggcaaa gaaatttgac ctggaccagt 1080
tgataactca tgtcttacca tttaaaaaaa tcagtgaagg atttgagctg ctcaattcag 1140
gacaaagcat tcgaacggtc ctgacgtttt gagatccaaa gtggcaggag gtctgtgttg 1200
tcatggtgaa ctggagtttc tcttgtgaga gttccctcat ctgaaatcat gtatctgtct 1260
cacaaataca agcataagta gaagatttgt tgaagacata gaacccttat aaagaattat 1320
taacctttat aaacatttaa agtcttgtga gcacctggga attagtataa taacaatgtt 1380
aatatttttg atttacattt tgtaaggcta taattgtatc ttttaagaaa acatacactt 1440
ggatttctat gttgaaatgg agatttttaa gagtttaac cagctgctgc agatatatat 1500
ctcaaaacag atatagcgta taaagatata gtaaatgcat ctcctagagt aatattcact 1560
taacacattg aaactattat tttttagatt tgaatataaa tgtatttttt aaacacttgt 1620
tatgagttaa cttggattac attttgaaat cagttcattc catgatgcat attactggat 1680
tagattaaga aagacagaaa agattaaggg acgggcacat ttttcaacga ttaagaatca 1740
tcattacata acttggtgaa actgaaaaag tatatcatat gggtacacaa ggctatttgc 1800
cagcatatat taatatttta gaaaatattc cttttgtaat actgaatata aacatagagc 1860
tagaatcata ttatcatact tatcataatg ttcaatttga tacagtagaa ttgcaagtcc 1920
ttaagtccct attcactgtg cttagtagtg actccattta ataaaaagtg tttttagttt 1980
ttaacaacta cactgatgta tttatatata tttataacat gttaaaaatt tttaaggaaa 2040
ttaaaaatta tataaaaaaa aaaaaaaaaa ctcgag 2076

<210> 79
<211> 2790
<212> DNA
<213> Homo sapien

<400> 79
aagcagttga gtaggcagaa aaaagaacct cttcattaag gattaaaatg tataggccag 60
cacgtgtaac ttcgacttca agatttctga atccatatgt agtatgtttc attgtcgtcg 120
caggggtagt gatcctggca gtcaccatag ctctacttgt ttacttttta gcttttgatc 180
aaaaatctta cttttatagg agcagttttc aactcctaaa tgttgaatat aatagtcagt 240
taaattcacc agctacacag gaatacagga ctttgagtgg aagaattgaa tctctgatta 300
ctaaaacatt caaagaatca aatttaagaa atcagttcat cagagctcat gttgccaaac 360
tgaggcaaga tggtagtggt gtgagagcgg atgttgtcat gaaatttcaa ttcactagaa 420
ataacaatgg agcatcaatg aaaagcagaa ttgagtctgt tttacgacaa atgctgaata 480
actctggaaa cctggaaata aacccttcaa ctgagataac atcacttact gaccaggctg 540
cagcaaattg gcttattaat gaatgtgggg ccggtccaga cctaataaca ttgtctgagc 600
agagaatcct tggaggcact gaggctgagg agggaagctg gccgtggcaa gtcagtctgc 660
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<210> 80
<211> 1460
<212> DNA
<213> Homo sapien

<400> 80
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<210> 81
<211> 386
<212> PRT
<213> Homo sapien

<400> 81

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Pro Phe Ser Ile Glu Glu Ile Glu Val Ala Pro Pro Lys Thr Lys Glu
        35                  40                  45
Val Arg Ile Lys Ile Leu Ala Thr Gly Ile Cys Arg Thr Asp Asp His
    50                  55                  60
Val Ile Lys Gly Thr Met Val Ser Lys Phe Pro Val Ile Val Gly His
65                  70                  75                  80
Glu Ala Thr Gly Ile Val Glu Ser Ile Gly Glu Gly Val Thr Thr Val
                85                  90                  95
Lys Pro Gly Asp Lys Val Ile Pro Leu Phe Leu Pro Gln Cys Arg Glu
            100                 105                 110
Cys Asn Ala Cys Arg Asn Pro Asp Gly Asn Leu Cys Ile Arg Ser Asp
        115                 120                 125
Ile Thr Gly Arg Gly Val Leu Ala Asp Gly Thr Thr Arg Phe Thr Cys
    130                 135                 140
Lys Gly Lys Pro Val His His Phe Met Asn Thr Ser Thr Phe Thr Glu
145                 150                 155                 160
Tyr Thr Val Val Asp Glu Ser Ser Val Ala Lys Ile Asp Asp Ala Ala
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Pro Pro Glu Lys Val Cys Leu Ile Gly Cys Gly Phe Ser Thr Gly Tyr
            180                 185                 190
Gly Ala Ala Val Lys Thr Gly Lys Val Lys Pro Gly Ser Thr Cys Val
        195                 200                 205
Val Phe Gly Leu Arg Gly Val Gly Leu Ser Val Ile Met Gly Cys Lys
    210                 215                 220
Ser Ala Gly Ala Ser Arg Ile Ile Gly Ile Asp Leu Asn Lys Asp Lys
225                 230                 235                 240
Phe Glu Lys Ala Met Ala Val Gly Ala Thr Glu Cys Ile Ser Pro Lys
                245                 250                 255
Asp Ser Thr Lys Pro Ile Ser Glu Val Leu Ser Glu Met Thr Gly Asn
            260                 265                 270
Asn Val Gly Tyr Thr Phe Glu Val Ile Gly His Leu Glu Thr Met Ile
        275                 280                 285
Asp Ala Leu Ala Ser Cys His Met Asn Tyr Gly Thr Ser Val Val Val
    290                 295                 300
Gly Val Pro Pro Ser Ala Lys Met Leu Thr Tyr Asp Pro Met Leu Leu
305                 310                 315                 320
Phe Thr Gly Arg Thr Trp Lys Gly Cys Val Phe Gly Gly Leu Lys Ser
                325                 330                 335
Arg Asp Asp Val Pro Lys Leu Val Thr Glu Phe Leu Ala Lys Lys Phe
            340                 345                 350
Asp Leu Asp Gln Leu Ile Thr His Val Leu Pro Phe Lys Lys Ile Ser
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Glu Gly Phe Glu Leu Leu Asn Ser Gly Gln Ser Ile Arg Thr Val Leu
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Thr Phe
385
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<210> 82
<211> 418
<212> PRT
<213> Homo sapien

<400> 82

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Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
        35                  40                  45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
    50                  55                  60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65                  70                  75                  80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
                85                  90                  95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
            100                 105                 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
        115                 120                 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
    130                 135                 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145                 150                 155                 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
                165                 170                 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
            180                 185                 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
        195                 200                 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
    210                 215                 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225                 230                 235                 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
                245                 250                 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
            260                 265                 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
        275                 280                 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
    290                 295                 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305                 310                 315                 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
                325                 330                 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
            340                 345                 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
        355                 360                 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
    370                 375                 380
Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385                 390                 395                 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
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<210> 83
<211> 418
<212> PRT
<213> Homo sapien

<400> 83
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Thr Ile Ala Leu Leu Val Tyr Phe Leu Ala Phe Asp Gln Lys Ser Tyr
35 40 45
Phe Tyr Arg Ser Ser Phe Gln Leu Leu Asn Val Glu Tyr Asn Ser Gln
50 55 60
Leu Asn Ser Pro Ala Thr Gln Glu Tyr Arg Thr Leu Ser Gly Arg Ile
65 70 75 80
Glu Ser Leu Ile Thr Lys Thr Phe Lys Glu Ser Asn Leu Arg Asn Gln
85 90 95
Phe Ile Arg Ala His Val Ala Lys Leu Arg Gln Asp Gly Ser Gly Val
100 105 110
Arg Ala Asp Val Val Met Lys Phe Gln Phe Thr Arg Asn Asn Asn Gly
115 120 125
Ala Ser Met Lys Ser Arg Ile Glu Ser Val Leu Arg Gln Met Leu Asn
130 135 140
Asn Ser Gly Asn Leu Glu Ile Asn Pro Ser Thr Glu Ile Thr Ser Leu
145 150 155 160
Thr Asp Gln Ala Ala Ala Asn Trp Leu Ile Asn Glu Cys Gly Ala Gly
165 170 175
Pro Asp Leu Ile Thr Leu Ser Glu Gln Arg Ile Leu Gly Gly Thr Glu
180 185 190
Ala Glu Glu Gly Ser Trp Pro Trp Gln Val Ser Leu Arg Leu Asn Asn
195 200 205
Ala His His Cys Gly Gly Ser Leu Ile Asn Asn Met Trp Ile Leu Thr
210 215 220
Ala Ala His Cys Phe Arg Ser Asn Ser Asn Pro Arg Asp Trp Ile Ala
225 230 235 240
Thr Ser Gly Ile Ser Thr Thr Phe Pro Lys Leu Arg Met Arg Val Arg
245 250 255
Asn Ile Leu Ile His Asn Asn Tyr Lys Ser Ala Thr His Glu Asn Asp
260 265 270
Ile Ala Leu Val Arg Leu Glu Asn Ser Val Thr Phe Thr Lys Asp Ile
275 280 285
His Ser Val Cys Leu Pro Ala Ala Thr Gln Asn Ile Pro Pro Gly Ser
290 295 300
Thr Ala Tyr Val Thr Gly Trp Gly Ala Gln Glu Tyr Ala Gly His Thr
305 310 315 320
Val Pro Glu Leu Arg Gln Gly Gln Val Arg Ile Ile Ser Asn Asp Val
325 330 335
Cys Asn Ala Pro His Ser Tyr Asn Gly Ala Ile Leu Ser Gly Met Leu
340 345 350
Cys Ala Gly Val Pro Gln Gly Gly Val Asp Ala Cys Gln Gly Asp Ser
355 360 365
Gly Gly Pro Leu Val Gln Glu Asp Ser Arg Arg Leu Trp Phe Ile Val
370 375 380

Gly Ile Val Ser Trp Gly Asp Gln Cys Gly Leu Pro Asp Lys Pro Gly
385 390 395 400
Val Tyr Thr Arg Val Thr Ala Tyr Leu Asp Trp Ile Arg Gln Gln Thr
405 410 415
Gly Ile

<210> 84
<211> 489
<212> DNA
<213> Homo sapien

<400> 84
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aattacagag gagtttcatg gcactaagtc aagatattca gaaaacaata aagaagacag 180
cacgtcggga gcagcttatg agagaagaag ctgaacagaa acgtttaaaa actgtacttg 240
agctacagta tgttttggac aaattgggag atgatgaagt gcggactgac ctgaaacaag 300
gtttgaatgg agtgccaata ttgtccgaag aggagttgtc attgttggat gaattctata 360
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aagttctaa 489

<210> 85
<211> 304
<212> DNA
<213> Homo sapien

<400> 85
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aggtcatctc caaatctaag ggaaaccttg agaagatgtg ccgcacactg gaggaccaag 240
tgagtgagct gaagacccag gaggaggaac agcagcggct gatcaatgaa ctgactgcgc 300
agag 304

<210> 86
<211> 296
<212> DNA
<213> Homo sapien

<400> 86
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tccatatgtt gtatgtttcc ttgtcctccc aggggttgtg atcctggcag tccccatagc 180
tctacttgtt tacttttag cttttgatca aaaatcttac ttttattgga gcaattttcc 240
actcccaaat gttgaatata atagtccgtt taattccccc gcttcaccgg gaattc 296

<210> 87
<211> 904
<212> DNA
<213> Homo sapien

<400> 87
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tatctgatcg ttctaaaaaa gagttgtccc cggttttaac cagtgaagtt catagtgttc 180
gtgcaggacg gcatcttgct accaaattga atattttagt acagcaacat tttgacttgg 240

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cacctgtaga tgtaaatagt agaccttcct cctgccttac taattttctt ctaaatggtc 540
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<210> 88
<211> 387
<212> DNA
<213> Homo sapien

<400> 88
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ccgctgcgat tcagaagatg ttggatgaca ataaccatct tattcagtgt ataatggact 180
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cacccacaca gaatatgcct atgggtcctg gagggatgaa tcagagcggg cctcccccac 360
ctccacgctc tcacaacatg ccttcaa 387

<210> 89
<211> 481
<212> DNA
<213> Homo sapien

<400> 89
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<210> 90
<211> 491
<212> DNA
<213> Homo sapien

<400> 90
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tggaaaaggg tgaccctaag aatgactcct ggatctttgc cctggctgtg ctcctgtgca 420
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atgtgacgga c 491

<210> 91
<211> 488
<212> DNA
<213> Homo sapien

<400> 91
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tcttcaccac catggagaag gctggggctc atttgcaggg gggagccaaa agggtcatca 420
tctctgcccc tctgctgatg ccccatgttc gtcatgggtg tgaaccatga gaagtatgac 480
acagcctc 488

<210> 92
<211> 384
<212> DNA
<213> Homo sapien

<400> 92
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ggaaggtgaa ggtcggagtc aacggatttg gtcgtattgg gcgcctggtc accagggctg 120
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tcaccaccat ggagaaggct gggg 384

<210> 93
<211> 162
<212> PRT
<213> Homo sapien

<400> 93
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20 25 30
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35 40 45
Ser Gln Asp Ile Gln Lys Thr Ile Lys Lys Thr Ala Arg Arg Glu Gln
50 55 60
Leu Met Arg Glu Glu Ala Glu Gln Lys Arg Leu Lys Thr Val Leu Glu
65 70 75 80
Leu Gln Tyr Val Leu Asp Lys Leu Gly Asp Asp Glu Val Arg Thr Asp
85 90 95
Leu Lys Gln Gly Leu Asn Gly Val Pro Ile Leu Ser Glu Glu Glu Leu
100 105 110
Ser Leu Leu Asp Glu Phe Tyr Lys Leu Val Asp Pro Glu Arg Asp Met
115 120 125
Ser Leu Arg Leu Asn Glu Gln Tyr Glu His Ala Ser Ile His Leu Trp
130 135 140
Asp Leu Leu Glu Gly Lys Glu Lys Pro Val Cys Gly Thr Thr Tyr Lys
145 150 155 160
Val Leu

<210> 94
<211> 100
<212> PRT
<213> Homo sapien

<400> 94
Asp Leu Glu Glu Ala Thr Leu Gln His Glu Ala Thr Ala Ala Thr Leu
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20 25 30
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35 40 45
Lys Met Glu Ile Asp Asp Leu Ala Cys Asn Met Glu Val Ile Ser Lys
50 55 60
Ser Lys Gly Asn Leu Glu Lys Met Cys Arg Thr Leu Glu Asp Gln Val
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Ser Glu Leu Lys Thr Gln Glu Glu Glu Gln Gln Arg Leu Ile Asn Glu
85 90 95
Leu Thr Ala Gln
100

<210> 95
<211> 99
<212> PRT
<213> Homo sapien

<400> 95
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Lys Arg Thr Ser Ser Leu Arg Ile Lys Met Phe Arg Ala Thr Arg Val
20 25 30
Thr Ser Thr Ser Arg Phe Leu Asn Pro Tyr Val Val Cys Phe Leu Val
35 40 45
Leu Pro Gly Val Val Ile Leu Ala Val Pro Ile Ala Leu Leu Val Tyr
50 55 60
Phe Leu Ala Phe Asp Gln Lys Ser Tyr Phe Tyr Trp Ser Asn Phe Pro
65 70 75 80
Leu Pro Asn Val Glu Tyr Asn Ser Pro Phe Asn Ser Pro Ala Ser Pro
85 90 95
Gly Ile Pro

<210> 96
<211> 257
<212> PRT
<213> Homo sapien

<400> 96
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His Leu Met Gln Ile Gln Lys Cys Glu Leu Val Leu Ile His Thr Tyr
20 25 30
Pro Val Gly Glu Asp Ser Leu Val Ser Asp Arg Ser Lys Lys Glu Leu
35 40 45
Ser Pro Val Leu Thr Ser Glu Val His Ser Val Arg Ala Gly Arg His
50 55 60

```
Leu Ala Thr Lys Leu Asn Ile Leu Val Gln Gln His Phe Asp Leu Ala
65                  70                  75                  80
Ser Thr Thr Ile Thr Asn Ile Pro Met Lys Glu Glu Gln His Ala Asn
                85                  90                  95
Thr Ser Ala Asn Tyr Asp Val Glu Leu Leu His His Lys Asp Ala His
            100                 105                 110
Val Asp Phe Leu Lys Ser Gly Asp Ser His Leu Gly Gly Gly Ser Arg
        115                 120                 125
Glu Gly Ser Phe Lys Glu Thr Ile Thr Leu Lys Trp Cys Thr Pro Arg
    130                 135                 140
Thr Asn Asn Ile Glu Leu His Tyr Cys Thr Gly Ala Tyr Arg Ile Ser
145                 150                 155                 160
Pro Val Asp Val Asn Ser Arg Pro Ser Ser Cys Leu Thr Asn Phe Leu
                165                 170                 175
Leu Asn Gly Arg Ser Val Leu Leu Glu Gln Pro Arg Lys Ser Gly Ser
            180                 185                 190
Lys Val Ile Ser His Met Leu Ser Ser His Gly Gly Glu Ile Phe Leu
        195                 200                 205
His Val Leu Ser Ser Ser Arg Ser Ile Leu Glu Asp Pro Pro Ser Ile
    210                 215                 220
Ser Glu Gly Cys Gly Gly Arg Val Thr Asp Tyr Arg Ile Thr Asp Phe
225                 230                 235                 240
Gly Glu Phe Met Arg Gly Lys Gln Ile Asn Ser Phe Ser Thr Pro Gln
                245                 250                 255
Ile
```

<210> 97
<211> 128
<212> PRT
<213> Homo sapien

<400> 97

```
Ser Leu Pro Gln Phe Ala Val His Pro Glu Arg Ser Gly Leu Ala Asp
 1               5                  10                  15
Ser Gly Asp Gly Gly Asn Met Ser Val Ala Phe Ala Ala Pro Arg Gln
            20                  25                  30
Arg Gly Lys Gly Glu Ile Thr Pro Ala Ala Ile Gln Lys Met Leu Asp
        35                  40                  45
Asp Asn Asn His Leu Ile Gln Cys Ile Met Asp Ser Gln Asn Lys Gly
    50                  55                  60
Lys Thr Ser Glu Cys Ser Gln Tyr Gln Gln Met Leu His Thr Asn Leu
65                  70                  75                  80
Val Tyr Leu Ala Thr Ile Ala Asp Ser Asn Gln Asn Met Gln Ser Leu
                85                  90                  95
Leu Pro Ala Pro Pro Thr Gln Asn Met Pro Met Gly Pro Gly Gly Met
            100                 105                 110
Asn Gln Ser Gly Pro Pro Pro Pro Pro Arg Ser His Asn Met Pro Ser
        115                 120                 125
```

<210> 98
<211> 159
<212> PRT
<213> Homo sapien

<400> 98

```
Phe Leu Asp Leu Arg Cys Tyr Arg Ala Gly Ser Ser Arg Leu Ala Val
 1               5                  10                  15
```

```
Ala Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu
            20                  25                  30
Asn Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu
        35                  40                  45
Glu Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr
    50                  55                  60
Arg Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His
65                  70                  75                  80
Gly Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp
                85                  90                  95
Met Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu
            100                 105                 110
Leu Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn
        115                 120                 125
Asp Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val
    130                 135                 140
Tyr Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu
145                 150                 155
```

<210> 99
<211> 147
<212> PRT
<213> Homo sapien

<400> 99

```
Met Glu Ser Gly Pro Lys Met Leu Ala Pro Val Cys Leu Val Glu Asn
 1               5                  10                  15
Asn Asn Glu Gln Leu Leu Val Asn Gln Gln Ala Ile Gln Ile Leu Glu
            20                  25                  30
Lys Ile Ser Gln Pro Val Val Val Val Ala Ile Val Gly Leu Tyr Arg
        35                  40                  45
Thr Gly Lys Ser Tyr Leu Met Asn His Leu Ala Gly Gln Asn His Gly
    50                  55                  60
Phe Pro Leu Gly Ser Thr Val Gln Ser Glu Thr Lys Gly Ile Trp Met
65                  70                  75                  80
Trp Cys Val Pro His Pro Ser Lys Pro Asn His Thr Leu Val Leu Leu
                85                  90                  95
Asp Thr Glu Gly Leu Gly Asp Val Glu Lys Gly Asp Pro Lys Asn Asp
            100                 105                 110
Ser Trp Ile Phe Ala Leu Ala Val Leu Leu Cys Ser Thr Phe Val Tyr
        115                 120                 125
Asn Ser Met Ser Thr Ile Asn His Gln Ala Leu Glu Gln Leu His Tyr
    130                 135                 140
Val Thr Asp
145
```

<210> 100
<211> 124
<212> PRT
<213> Homo sapien

<400> 100

```
Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile Gly Arg
 1               5                  10                  15
Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile Val Ala
            20                  25                  30
Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met Phe Gln
        35                  40                  45
```

```
Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala Glu Asn
    50                  55                  60
Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln Glu Arg
65                  70                  75                  80
Asp Pro Ser Lys Ile Lys Trp Gly Asp Ala Gly Ala Glu Tyr Val Val
                85                  90                  95
Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly Ala His Leu
            100                 105                 110
Gln Gly Gly Ala Lys Arg Val Ile Ile Ser Ala Pro
        115                 120
```

<210> 101
<211> 127
<212> PRT
<213> Homo sapien

<400> 101

```
Gln Ser Ala Ala Ser Ser Phe Ala Ser Pro Ala Glu Pro His Arg Ser
 1               5                  10                  15
Asp Thr Met Gly Lys Val Lys Val Gly Val Asn Gly Phe Gly Arg Ile
            20                  25                  30
Gly Arg Leu Val Thr Arg Ala Ala Phe Asn Ser Gly Lys Val Asp Ile
        35                  40                  45
Val Ala Ile Asn Asp Pro Phe Ile Asp Leu Asn Tyr Met Val Tyr Met
    50                  55                  60
Phe Gln Tyr Asp Ser Thr His Gly Lys Phe His Gly Thr Val Glu Ala
65                  70                  75                  80
Glu Asn Gly Lys Leu Val Ile Asn Gly Asn Pro Ile Thr Ile Phe Gln
                85                  90                  95
Glu Arg Asp Pro Ser Lys Ile Lys Trp Gly Asp Thr Gly Ala Glu Tyr
            100                 105                 110
Val Val Glu Ser Thr Gly Val Phe Thr Thr Met Glu Lys Ala Gly
        115                 120                 125
```

<210> 102
<211> 1225
<212> DNA
<213> Homo sapien

<400> 102

```
atggcggcgc ggtcgtcgtc gggggtggcg gcggcagagg gggcggcggc cctggcggca      60
gcggagacgg cagccgtgac ggtggcagcg gcggcgcggg acctgggcct gggggaatga     120
ggcggccgcg gcgggccagc ggcggagccg tgtagcggag aagctccccc tccctgcttc     180
ccttggccga gccgggggcg cgcgcgcacg cggccgtcca gagcgggctc cccacccctc     240
gactcctgcg acccgcaccg cacccccacc cgggcccgga ggatgatgaa gctcaagtcg     300
aaccagaccc gcacctacga cggcgacggc tacaagaagc gggccgcatg cctgtgtttc     360
cgcagcgaga gcgaggagga ggtgctactc gtgagcagta gtcgccatcc agacagatgg     420
attgtccctg gaggaggcat ggagcccgag gaggagccaa gtgtggcagc agttcgtgaa     480
gtctgtgagg aggctggagt aaaagggaca ttgggaagat tagttggaat ttttgagaac     540
caggagagga agcacaggac gtatgtctat gtgctcattg tcactgaagt gctggaagac     600
tgggaagatt cagttaacat tggaaggaag agggaatggt ttaaaataga agacgccata     660
aaagtgctgc agtatcacaa acccgtgcag gcatcatatt ttgaaacatt gaggcaaggc     720
tactcagcca acaatggcac cccagtcgtg gccaccacat actcggtttc tgctcagagc     780
tcgatgtcag gcatcagatg actgaagact tcctgtaaga gaaatggaaa ttggaaacta     840
gactgaagtg caaatcttcc ctctcaccct ggctctttcc acttctcaca ggcctcctct     900
ttcaaataag gcatggtggg cagcaaagaa agggtgtatt gataatgttg ctgtttggtg     960
ttaagtgatg gggctttttc ttctgttttt attgagggtg ggggttgggt gtgtaatttg    1020
taagtacttt tgtgcatgat ctgtccctcc ctcttcccac ccctgcagtc ctctgaagag    1080
```

aggccaacag ccttcccctg ccttggattc tgaagtgttc ctgtttgtct tatcctggcc 1140
ctggccagac gttttctttg atttttaatt ttttttttt attaaaagat accagtatga 1200
gaaaaaaaaa aaaaaaaaac tcgag 1225

<210> 103
<211> 741
<212> DNA
<213> Homo sapien

<400> 103
agaaacctca atcggattca gcaaaggaat ggtgttatta tcactacata ccaaatgtta 60
atcaataact ggcagcaact ttcaagcttt aggggccaag agtttgtgtg ggactatgtc 120
atcctcgatg aagcacataa aataaaaacc tcatctacta agtcagcaat atgtgctcgt 180
gctattcctg caagtaatcg cctcctcctc acaggaaccc caatccagaa taatttacaa 240
gaactatggt ccctatttga ttttgcttgt caagggtccc tgctgggaac attaaaaact 300
tttaagatgg agtatgaaaa tcctattact agagcaagag agaaggatgc taccccagga 360
gaaaaagcct tgggatttaa aatatctgaa aacttaatgg caatcataaa accctatttt 420
ctcaggagga ctaaagaaga cgtacagaag aaaaagtcaa gcaacccaga ggccagactt 480
aatgaaaaga atccagatgt tgatgccatt tgtgaaatgc cttccctttc caggagaaat 540
gatttaatta tttggatacg acttgtgcct ttacaagaag aaatatacag gaaatttgtg 600
tctttagatc atatcaagga gttgctaatg gagacgcgct caccttggc tgagctaggt 660
gtcttaaaga agctgtgtga tcatcctagg ctgctgtctg cacgggcttg ttgtttgcta 720
aatcttggga cattctctgc t 741

<210> 104
<211> 321
<212> DNA
<213> Homo sapien

<400> 104
ttgctctgcg tcatcaaaga caccaaactg ctgtgctata aaagttccaa ggaccagcag 60
cctcagatgg aactgccact ccaaggctgt aacattacgt acatcccgaa agacagcaaa 120
aagaagaagc acgagctgaa gattactcag cagggcacgg acccgcttgt tctcgccgtc 180
cagagcaagg aacaggccga gcagtggctg aaggtgatca aagaagccta cagtggttgt 240
agtggccccg tggattcaga gtgtcctcct ccaccaagct ccccggtgca caaggcagaa 300
ctggagaaga aactgtcttc a 321

<210> 105
<211> 389
<212> DNA
<213> Homo sapien

<400> 105
cagcactggc cacactataa aattcaggtt cagaaaaaca gggtaagtca cagacagcaa 60
cgcttccagc atttattttc tttgcaccca tgggcaattt gagaaaattt acctttagaa 120
cgaactctgt taaaggtaca gacagtacaa tacttttttat tcagaaggtt tctgcataaa 180
ggtgatagtc ttttgactta atatattatt gtctcctgcc ttgtgtttct ggaatgaatg 240
aaggtcatta tttagaagat aatctgggtt gtatttgtgt cgtcagattg aattttcatt 300
gcacatgcta cttaatgtct ttaccaaata ataacaaagg gaaagaaaac caaatataga 360
tgtataataa ggaaaagctg gcctataga 389

<210> 106
<211> 446
<212> DNA
<213> Homo sapien

<400> 106
gccacatttg ccctggtcat agtttaaaca ccaggtcctg tgtcacatct ttttggtgcc 60

acaagtatca ctccattgtt cagagagtaa tgtattagtt ctgcccaatt cattcttcac 120
ttttatttct tccatttcat tagcatttat atcagctcaa gaagttaagg ttagaaaatt 180
ttccacttca aattttcagt acagaaatgt gctgtgatgt ttgacaagac tatttcatag 240
taagtgagtt aatgtttatt ggcctctgct ctcctctgtg tcagacctag gaagcctgag 300
gattacttag ttgttctgtc tctgggtcca caggcagaat ttggcccatc caaagactgg 360
ccaagtgcca aaaaaaggcc tgattaggcc ctgaaattca gtgaaattct gcctgaagaa 420
acctcttatt gaatttgaaa accata 446

<210> 107
<211> 467
<212> DNA
<213> Homo sapien

<400> 107
ccgccgctgc cgtcgccttc ctgggattgg agtctcgagc tttcttcgtt cgttcgccgg 60
cgggttcgcg cccttctcgc gcctcggggc tgcgaggctg gggaaggggt tggagggggc 120
tgttgatcgc cgcgtttaag ttgcgctcgg ggcggccatg tcggccggcg aggtcgagcg 180
cctagtgtcg gagctgagcg gcgggaccgg aggggatgag gaggaagagt ggctctatgg 240
cgatgaagat gaagttgaaa ggccagaaga agaaaatgcc agtgctaatc ctccatctgg 300
aattgaagat gaaactgctg aaaatggtgt accaaaaccg aaagtgactg agaccgaaga 360
tgatagtgat agtgacagcg atgatgatga agatgatgtg catgtcacta taggagacat 420
taaaacggga gcaccacagt atgggagtta tggtacagca cctgtaa 467

<210> 108
<211> 491
<212> DNA
<213> Homo sapien

<400> 108
gaaagataca acttccccaa cccaaacccg tttgtggagg acgacatgga taagaatgaa 60
atcgcctctg ttgcgtaccg ttaccgcagg tggaagcttg gagatgatat tgaccttatt 120
gtccgttgtg agcacgatgg cgtcatgact ggagccaacg gggaagtgtc cttcatcaac 180
atcaagacac tcaatgagtg ggattccagg cactgtaatg gcgttgactg gcgtcagaag 240
ctggactctc agcgaggggc tgtcattgcc acggagctga agaacaacag ctacaagttg 300
gcccggtgga cctgctgtgc tttgctggct ggatctgagt acctcaagct tggttatgtg 360
tctcggtacc acgtgaaaga ctcctcacgc cacgtcatcc taggcaccca gcagttcaag 420
cctaatgagt ttgccagcca gatcaacctg agcgtggaga atgcctgagg cattttacgc 480
tgcgtcattg a 491

<210> 109
<211> 489
<212> DNA
<213> Homo sapien

<400> 109
ctcagatagt actgaaccct ttatcaacta tgtttttca gtctgacaac caaggcggct 60
actaagtgac taaggggcag gtagtataca gtgtggataa gcaggacaaa ggggtgattc 120
acatcccagg caggacagag caggagatca tgagatttca tcactcagga tggcttgtga 180
tttatttat tttattcttt ttttttttg agatggagtc tcactcttgc ccaggctgga 240
gtgcagtggt gcgatcttgg ctcactgcaa cctctgcctc ctgggttcaa gcagttctcc 300
tgcctcagcc tcccaagtag ctgggattac aggcgtccgc caccatgccc agccaatttt 360
tgtactttta gtagagatgg ggtttcacca tgttggccag gctggtctcg aactcctgac 420
ctcaggtgat ccactcgcct cggcctccca aagtgctggg attataggca tgcgccacca 480
tgcccgggc 489

<210> 110
<211> 391
<212> DNA

<213> Homo sapien

<400> 110

gcggagtccg ctggctgacc cgagcgctgg tctccgccgg gaaccctggg gcatggagag 60
gtctgagtac ctcggccgcg gcgcacgctg catcgcggag ccaggctgcc gctgtcccag 120
tggagttcca ggagcaccac ctgagtgagg tgcagaatat ggcatctgag gagaagctgg 180
agcaggtgct gagttccatg aaggagaaca aagtggccat cattggaaag attcataccc 240
cgatggagta taaggggggag ctagcctcct atgatatgcg gctgaggcgt aagttggact 300
tatttgccaa cgtaatccat gtgaagtcac ttcctgggta tatgactcgg cacaacaatc 360
tagacctggt gatcattcga gagcagacag a 391

<210> 111
<211> 172
<212> PRT
<213> Homo sapien

<400> 111

Met Met Lys Leu Lys Ser Asn Gln Thr Arg Thr Tyr Asp Gly Asp Gly
1 5 10 15
Tyr Lys Lys Arg Ala Ala Cys Leu Cys Phe Arg Ser Glu Ser Glu Glu
20 25 30
Glu Val Leu Leu Val Ser Ser Ser Arg His Pro Asp Arg Trp Ile Val
35 40 45
Pro Gly Gly Gly Met Glu Pro Glu Glu Glu Pro Ser Val Ala Ala Val
50 55 60
Arg Glu Val Cys Glu Glu Ala Gly Val Lys Gly Thr Leu Gly Arg Leu
65 70 75 80
Val Gly Ile Phe Glu Asn Gln Glu Arg Lys His Arg Thr Tyr Val Tyr
85 90 95
Val Leu Ile Val Thr Glu Val Leu Glu Asp Trp Glu Asp Ser Val Asn
100 105 110
Ile Gly Arg Lys Arg Glu Trp Phe Lys Ile Glu Asp Ala Ile Lys Val
115 120 125
Leu Gln Tyr His Lys Pro Val Gln Ala Ser Tyr Phe Glu Thr Leu Arg
130 135 140
Gln Gly Tyr Ser Ala Asn Asn Gly Thr Pro Val Val Ala Thr Thr Tyr
145 150 155 160
Ser Val Ser Ala Gln Ser Ser Met Ser Gly Ile Arg
165 170

<210> 112
<211> 247
<212> PRT
<213> Homo sapien

<400> 112

Arg Asn Leu Asn Arg Ile Gln Gln Arg Asn Gly Val Ile Ile Thr Thr
1 5 10 15
Tyr Gln Met Leu Ile Asn Asn Trp Gln Gln Leu Ser Ser Phe Arg Gly
20 25 30
Gln Glu Phe Val Trp Asp Tyr Val Ile Leu Asp Glu Ala His Lys Ile
35 40 45
Lys Thr Ser Ser Thr Lys Ser Ala Ile Cys Ala Arg Ala Ile Pro Ala
50 55 60
Ser Asn Arg Leu Leu Leu Thr Gly Thr Pro Ile Gln Asn Asn Leu Gln
65 70 75 80
Glu Leu Trp Ser Leu Phe Asp Phe Ala Cys Gln Gly Ser Leu Leu Gly
85 90 95

```
Thr Leu Lys Thr Phe Lys Met Glu Tyr Glu Asn Pro Ile Thr Arg Ala
            100                 105                 110
Arg Glu Lys Asp Ala Thr Pro Gly Glu Lys Ala Leu Gly Phe Lys Ile
        115                 120                 125
Ser Glu Asn Leu Met Ala Ile Ile Lys Pro Tyr Phe Leu Arg Arg Thr
    130                 135                 140
Lys Glu Asp Val Gln Lys Lys Lys Ser Ser Asn Pro Glu Ala Arg Leu
145                 150                 155                 160
Asn Glu Lys Asn Pro Asp Val Asp Ala Ile Cys Glu Met Pro Ser Leu
                165                 170                 175
Ser Arg Arg Asn Asp Leu Ile Ile Trp Ile Arg Leu Val Pro Leu Gln
            180                 185                 190
Glu Glu Ile Tyr Arg Lys Phe Val Ser Leu Asp His Ile Lys Glu Leu
        195                 200                 205
Leu Met Glu Thr Arg Ser Pro Leu Ala Glu Leu Gly Val Leu Lys Lys
    210                 215                 220
Leu Cys Asp His Pro Arg Leu Leu Ser Ala Arg Ala Cys Cys Leu Leu
225                 230                 235                 240
Asn Leu Gly Thr Phe Ser Ala
                245
```

<210> 113
<211> 107
<212> PRT
<213> Homo sapien

<400> 113

```
Leu Leu Cys Val Ile Lys Asp Thr Lys Leu Leu Cys Tyr Lys Ser Ser
 1               5                  10                  15
Lys Asp Gln Gln Pro Gln Met Glu Leu Pro Leu Gln Gly Cys Asn Ile
            20                  25                  30
Thr Tyr Ile Pro Lys Asp Ser Lys Lys Lys Lys His Glu Leu Lys Ile
        35                  40                  45
Thr Gln Gln Gly Thr Asp Pro Leu Val Leu Ala Val Gln Ser Lys Glu
    50                  55                  60
Gln Ala Glu Gln Trp Leu Lys Val Ile Lys Glu Ala Tyr Ser Gly Cys
65                  70                  75                  80
Ser Gly Pro Val Asp Ser Glu Cys Pro Pro Pro Pro Ser Ser Pro Val
                85                  90                  95
His Lys Ala Glu Leu Glu Lys Lys Leu Ser Ser
            100                 105
```

<210> 114
<211> 155
<212> PRT
<213> Homo sapien

<400> 114

```
Glu Arg Tyr Asn Phe Pro Asn Pro Asn Pro Phe Val Glu Asp Asp Met
 1               5                  10                  15
Asp Lys Asn Glu Ile Ala Ser Val Ala Tyr Arg Tyr Arg Arg Trp Lys
            20                  25                  30
Leu Gly Asp Asp Ile Asp Leu Ile Val Arg Cys Glu His Asp Gly Val
        35                  40                  45
Met Thr Gly Ala Asn Gly Glu Val Ser Phe Ile Asn Ile Lys Thr Leu
    50                  55                  60
Asn Glu Trp Asp Ser Arg His Cys Asn Gly Val Asp Trp Arg Gln Lys
65                  70                  75                  80
```

```
Leu Asp Ser Gln Arg Gly Ala Val Ile Ala Thr Glu Leu Lys Asn Asn
                85                  90                  95
Ser Tyr Lys Leu Ala Arg Trp Thr Cys Cys Ala Leu Leu Ala Gly Ser
            100                 105                 110
Glu Tyr Leu Lys Leu Gly Tyr Val Ser Arg Tyr His Val Lys Asp Ser
        115                 120                 125
Ser Arg His Val Ile Leu Gly Thr Gln Gln Phe Lys Pro Asn Glu Phe
    130                 135                 140
Ala Ser Gln Ile Asn Leu Ser Val Glu Asn Ala
145                 150                 155
```

<210> 115
<211> 129
<212> PRT
<213> Homo sapien

<400> 115

```
Gly Val Arg Trp Leu Thr Arg Ala Leu Val Ser Ala Gly Asn Pro Gly
 1               5                  10                  15
Ala Trp Arg Gly Leu Ser Thr Ser Ala Ala Ala His Ala Ala Ser Arg
            20                  25                  30
Ser Gln Ala Ala Ala Val Pro Val Glu Phe Gln Glu His His Leu Ser
        35                  40                  45
Glu Val Gln Asn Met Ala Ser Glu Glu Lys Leu Glu Gln Val Leu Ser
    50                  55                  60
Ser Met Lys Glu Asn Lys Val Ala Ile Ile Gly Lys Ile His Thr Pro
65                  70                  75                  80
Met Glu Tyr Lys Gly Glu Leu Ala Ser Tyr Asp Met Arg Leu Arg Arg
                85                  90                  95
Lys Leu Asp Leu Phe Ala Asn Val Ile His Val Lys Ser Leu Pro Gly
            100                 105                 110
Tyr Met Thr Arg His Asn Asn Leu Asp Leu Val Ile Ile Arg Glu Gln
        115                 120                 125
Thr
```

<210> 116
<211> 550
<212> DNA
<213> Homo sapien

<400> 116

```
gaattcggca ccagcctcag agccccccag cccggctacc acccccctgcg gaaaggtacc      60
catctgcatt cctgcccgtc gggacctggt ggacagtcca gcctccttgg cctctagcct     120
tggctcaccg ctgcctagag ccaaggagct catcctgaat gaccttcccg ccagcactcc     180
tgcctccaaa tcctgtgact cctccccgcc ccaggacgct tccaccccca ggcccagctc     240
ggccagtcac ctctgccagc ttgctgccaa gccagcacct tccacggaca gcgtcgccct     300
gaggagcccc ctgactctgt ccagtccctt caccacgtcc ttcagcctgg gctcccacag     360
cactctcaac ggagacctct ccgtgcccag ctcctacgtc agcctccacc tgtccccca      420
ggtcagcagc tctgtggtgt acggacgctc ccccgtgatg gcatttgagt ctcatcccca     480
tctccgaggg tcatccgtct cttcctccct acccagcatc cctgggggaa agccggccta     540
ctccttccac                                                           550
```

<210> 117
<211> 154
<212> DNA
<213> Homo sapien

<400> 117
ttctgaggga aagccgagtg gagtgggcga cccggcggcg gtgacaatga gttttcttgg 60
aggctttttt ggtcccattt gtgagattga tgttgccctt aatgatgggg aaaccaggaa 120
aatggcagaa atgaaaactg aggatggcaa agta 154

<210> 118
<211> 449
<212> DNA
<213> Homo sapien

<400> 118
gaattcggca ccagggcccg cagcccgagt gtcgccgcca tggcttcgcc gcagctctgc 60
cgcgcgctgg tgtcggcgca atgggtggcg gaggcgctgc gggccccgcg cgctgggcag 120
cctctgcagc tgctggacgc ctcctggtac ctgccgaagc tggggcgcga cgcgcgacgc 180
gagttcgagg agcgccacat cccgggcgcc gctttcttcg acatcgacca gtgcagcgac 240
cgcacctcgc cctacgacca catgctgccc ggggccgagc atttcgcgga gtacgcaggc 300
cgcctgggcg tgggcgcggc cacccacgtc gtgatctacg acgccagcga ccagggcctc 360
tactccgccc cgcgcgtctg gtggatgttc cgcgccttcg gccaccacgc cgtgtcactg 420
cttgatggcg gcctccgcca ctggctgcg 449

<210> 119
<211> 642
<212> DNA
<213> Homo sapien

<400> 119
gaattcggca cgagcagtaa cccgaccgcc gctggtcttc gctggacacc atgaatcaca 60
ctgtccaaac cttcttctct cctgtcaaca gtggccagcc ccccaactat gagatgctca 120
aggaggagca cgaggtggct gtgctggggg cgccccacaa ccctgctccc ccgacgtcca 180
ccgtgatcca catccgcagc gagacctccg tgcccgacca tgtcgtctgg tccctgttca 240
acaccctctt catgaacccc tgctgcctgg gcttcatagc attcgcctac tccgtgaagt 300
ctagggacag gaagatggtt ggcgacgtga ccggggccca ggcctatgcc tccaccgcca 360
agtgcctgaa catctgggcc ctgattctgg gcatcctcat gaccattctg ctcatcgtca 420
tcccagtgct gatcttccag gcctatggat agatcaggag gcatcactga ggccaggagc 480
tctgcccatg acctgtatcc cacgtactcc aacttccatt cctcgccctg cccccggagc 540
cgagtcctgt atcagccctt tatcctcaca cgcttttcta caatggcatt caataaagtg 600
cacgtgtttc tggtgaaaaa aaaaaaaaaa aaaaaactcg ag 642

<210> 120
<211> 603
<212> DNA
<213> Homo sapien

<400> 120
gaattcggca cgagccacaa cagccactac gactgcatcc actggatcca cggccacccc 60
gtcctccacc ccgggaacag ctccccctcc caaagtgctg accagcccgg ccaccacacc 120
catgtccacc atgtccacaa tccacacctc ctctactcca gagaccaccc acacctccac 180
agtgctgacc accacagcca ccatgacaag ggccaccaat tccacggcca caccctcctc 240
cactctgggg acgacccgga tcctcactga gctgaccaca acagccacta caactgcagc 300
cactggatcc acggccaccc tgtcctccac cccagggacc acctggatcc tcacagagcc 360
gagcactata gccaccgtga tggtgcccac cggttccacg gccaccgcct cctccactct 420
gggaacagct cacaccccca aagtggtgac caccatggcc actatgccca cagccactgc 480
ctccacggtt cccagctcgt ccaccgtggg gaccacccgc acccctgcag tgctccccag 540
cagcctgcca accttcagcg tgtccactgt gtcctcctca gtcctcacca ccctgagacc 600
cac 603

<210> 121
<211> 178

<212> PRT
<213> Homo sapien

<400> 121
Ser Glu Pro Pro Ser Pro Ala Thr Thr Pro Cys Gly Lys Val Pro Ile
1 5 10 15
Cys Ile Pro Ala Arg Arg Asp Leu Val Asp Ser Pro Ala Ser Leu Ala
20 25 30
Ser Ser Leu Gly Ser Pro Leu Pro Arg Ala Lys Glu Leu Ile Leu Asn
35 40 45
Asp Leu Pro Ala Ser Thr Pro Ala Ser Lys Ser Cys Asp Ser Ser Pro
50 55 60
Pro Gln Asp Ala Ser Thr Pro Arg Pro Ser Ser Ala Ser His Leu Cys
65 70 75 80
Gln Leu Ala Ala Lys Pro Ala Pro Ser Thr Asp Ser Val Ala Leu Arg
85 90 95
Ser Pro Leu Thr Leu Ser Ser Pro Phe Thr Thr Ser Phe Ser Leu Gly
100 105 110
Ser His Ser Thr Leu Asn Gly Asp Leu Ser Val Pro Ser Ser Tyr Val
115 120 125
Ser Leu His Leu Ser Pro Gln Val Ser Ser Ser Val Val Tyr Gly Arg
130 135 140
Ser Pro Val Met Ala Phe Glu Ser His Pro His Leu Arg Gly Ser Ser
145 150 155 160
Val Ser Ser Ser Leu Pro Ser Ile Pro Gly Gly Lys Pro Ala Tyr Ser
165 170 175
Phe His

<210> 122
<211> 36
<212> PRT
<213> Homo sapien

<400> 122
Met Ser Phe Leu Gly Gly Phe Phe Gly Pro Ile Cys Glu Ile Asp Val
1 5 10 15
Ala Leu Asn Asp Gly Glu Thr Arg Lys Met Ala Glu Met Lys Thr Glu
20 25 30
Asp Gly Lys Val
35

<210> 123
<211> 136
<212> PRT
<213> Homo sapien

<400> 123
Met Ala Ser Pro Gln Leu Cys Arg Ala Leu Val Ser Ala Gln Trp Val
1 5 10 15
Ala Glu Ala Leu Arg Ala Pro Arg Ala Gly Gln Pro Leu Gln Leu Leu
20 25 30
Asp Ala Ser Trp Tyr Leu Pro Lys Leu Gly Arg Asp Ala Arg Arg Glu
35 40 45
Phe Glu Glu Arg His Ile Pro Gly Ala Ala Phe Phe Asp Ile Asp Gln
50 55 60
Cys Ser Asp Arg Thr Ser Pro Tyr Asp His Met Leu Pro Gly Ala Glu
65 70 75 80

```
His Phe Ala Glu Tyr Ala Gly Arg Leu Gly Val Gly Ala Ala Thr His
                85                  90                  95
Val Val Ile Tyr Asp Ala Ser Asp Gln Gly Leu Tyr Ser Ala Pro Arg
            100                 105                 110
Val Trp Trp Met Phe Arg Ala Phe Gly His His Ala Val Ser Leu Leu
        115                 120                 125
Asp Gly Gly Leu Arg His Trp Leu
    130                 135
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<210> 124
<211> 133
<212> PRT
<213> Homo sapien

<400> 124

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Met Asn His Thr Val Gln Thr Phe Phe Ser Pro Val Asn Ser Gly Gln
 1               5                  10                  15
Pro Pro Asn Tyr Glu Met Leu Lys Glu Glu His Glu Val Ala Val Leu
            20                  25                  30
Gly Ala Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile
        35                  40                  45
Arg Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn
    50                  55                  60
Thr Leu Phe Met Asn Pro Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr
65                  70                  75                  80
Ser Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala
                85                  90                  95
Gln Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile
            100                 105                 110
Leu Gly Ile Leu Met Thr Ile Leu Leu Ile Val Ile Pro Val Leu Ile
        115                 120                 125
Phe Gln Ala Tyr Gly
    130
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<210> 125
<211> 195
<212> PRT
<213> Homo sapien

<400> 125

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Thr Thr Ala Thr Thr Thr Ala Ser Thr Gly Ser Thr Ala Thr Pro Ser
 1               5                  10                  15
Ser Thr Pro Gly Thr Ala Pro Pro Pro Lys Val Leu Thr Ser Pro Ala
            20                  25                  30
Thr Thr Pro Met Ser Thr Met Ser Thr Ile His Thr Ser Ser Thr Pro
        35                  40                  45
Glu Thr Thr His Thr Ser Thr Val Leu Thr Thr Thr Ala Thr Met Thr
    50                  55                  60
Arg Ala Thr Asn Ser Thr Ala Thr Pro Ser Ser Thr Leu Gly Thr Thr
65                  70                  75                  80
Arg Ile Leu Thr Glu Leu Thr Thr Thr Ala Thr Thr Thr Ala Ala Thr
                85                  90                  95
Gly Ser Thr Ala Thr Leu Ser Ser Thr Pro Gly Thr Thr Trp Ile Leu
            100                 105                 110
Thr Glu Pro Ser Thr Ile Ala Thr Val Met Val Pro Thr Gly Ser Thr
        115                 120                 125
Ala Thr Ala Ser Ser Thr Leu Gly Thr Ala His Thr Pro Lys Val Val
    130                 135                 140
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Thr Thr Met Ala Thr Met Pro Thr Ala Thr Ala Ser Thr Val Pro Ser
145 150 155 160
Ser Ser Thr Val Gly Thr Thr Arg Thr Pro Ala Val Leu Pro Ser Ser
165 170 175
Leu Pro Thr Phe Ser Val Ser Thr Val Ser Ser Ser Val Leu Thr Thr
180 185 190
Leu Arg Pro
195

<210> 126
<211> 509
<212> DNA
<213> Homo sapien

<400> 126
gaattcggca cgagccaagt acccccctgag gaatctgcag cctgcatctg agtacaccgt 60
atccctcgtg gccataaagg gcaaccaaga gagccccaaa gccactggag tctttaccac 120
actgcagcct gggagctcta ttccacctta caacaccgag gtgactgaga ccaccattgt 180
gatcacatgg acgcctgctc caagaattgg ttttaagctg ggtgtacgac caagccaggg 240
aggagaggca ccacgagaag tgacttcaga ctcaggaagc atcgttgtgt ccggcttgac 300
tccaggagta gaatacgtct acaccatcca agtcctgaga gatggacagg aaagagatgc 360
gccaattgta aacaaagtgg tgacaccatt gtctccacca acaaacttgc atctggaggc 420
aaaccctgac actggagtgc tcacagtctc ctggagagga gcaccacccc agacattact 480
gggtatagaa ttaccacaac ccctacaaa 509

<210> 127
<211> 500
<212> DNA
<213> Homo sapien

<400> 127
gaattcggca cgagccactg atgtccgggg agtcagccag gagcttgggg aagggaagcg 60
cgcccccggg gccggtcccg gagggctcga tccgcatcta cagcatgagg ttctgcccgt 120
ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat caggcatgaa gtcatcaata 180
tcaacctgaa aaataagcct gagtggttct ttaagaaaaa tccctttggt ctggtgccag 240
ttctggaaaa cagtcagggt cagctgatct acgagtctgc catcacctgt gagtacctgg 300
atgaagcata cccagggaag aagctgttgc cggatgaccc ctatgagaaa gcttgccaga 360
agatgatctt agagttgttt tctaaggtgc catccttggt aggaagcttt attagaagcc 420
aaaataaaga agactatgct ggcctaaaag aagaatttcg taaagaattt accaagctag 480
aggaggttct gactaataag 500

<210> 128
<211> 500
<212> DNA
<213> Homo sapien

<400> 128
agctttcctc tgctgccgct cggtcacgct tgtgcccgaa ggaggaaaca gtgacagacc 60
tggagactgc agttctctat ccttcacaca gctctttcac catgcctgga tcacttcctt 120
tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctattttc 180
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tggtgtagat gctggaaagt 240
ataccattgg cttgggccag gccaagatgg gcttctgcac agatagagaa gatattaact 300
ctctttgcat gactgtggtt cagaatctta tggagagaaa taacctttcc tatgattgca 360
ttgggcggct ggaagttgga acagagacaa tcatcgacaa atcaaagtct gtgaagacta 420
atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca 500

<210> 129

<211> 497
<212> DNA
<213> Homo sapien

<400> 129
gaattcggca cgagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct 60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120
cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
tacgtatgtt acctgga 497

<210> 130
<211> 383
<212> DNA
<213> Homo sapien

<400> 130
gaattcggca cgagggccgc ggctgccgac tgggtcccct gccgctgtcg ccaccatggc 60
tccgcaccgc cccgcgcccg cgctgctttg cgcgctgtcc ctggcgctgt gcgcgctgtc 120
gctgcccgtc cgcgcggcca ctgcgtcgcg gggggcgtcc caggcggggg cgccccaggg 180
gcgggtgccc gaggcgcggc ccaacagcat ggtggtggaa caccccgagt tcctcaaggc 240
agggaaggag cctggcctgc agatctggcg tgtggagaaa gttcgatctg gtggcccgtg 300
cccaccaacc tttatggaga cttcttcacg ggcgacgcct acgtcatcct gaagacagtg 360
cagcttaaga acggaaaatc ttg 383

<210> 131
<211> 509
<212> DNA
<213> Homo sapien

<400> 131
gaattcggca cgagagtcag ccgcatcttc ttttgcgtcg ccagccgagc cacatcgctc 60
agacaccatg gggaaggtga aggtcggagt caacggattt ggtcgtattg ggcgcctggt 120
caccagggct gcttttaact ctggtaaagt ggatattgtt gccatcaatg acccccttcat 180
tgacctcaac tacatggttt acatgttcca atatgattcc acccatggca aattccatgg 240
caccgtcaag gctgagaacg ggaagcttgt catcaatgga aatcccatca ccatcttcca 300
ggagcgagat ccctccaaaa tcaagtgggg cgatgctggc gctgagtacg tcgtggagtc 360
cactggccgt cttcaccacc atggagaagg ctggggctca tttgcagggg ggagccaaaa 420
gggtcatcat ctctgccccc tctgctgacg cccccatgtt cgtcatgggt gtgaaccatg 480
agaagtatga caacagcctc aagatcatc 509

<210> 132
<211> 357
<212> DNA
<213> Homo sapien

<400> 132
gaattcggca cgagtaagaa gaagccccta gaccacagct ccacaccatg gactggacct 60
ggaggatcct cttcttggtg gcagcagcaa caggtgccca ctcccaggtg caactggtgc 120
aatctgggtc tgagttgaag aagcctgggg cctcagtgaa ggtttcctgc aaggcttctg 180
gacacatctt cagtatctat ggtttgaatt gggtgcgaca ggcccctggt caaggccttg 240
agtggatggg atggatcaaa gtcgacactg cgaacccaac gtatgcccag ggcttcacag 300
gacgatttgt cttctccctg gacacctctg tcagcacggc atatctgcag atcagca 357

<210> 133
<211> 468
<212> DNA
<213> Homo sapien

<400> 133
gaattcggca cgaggcgccc cgaaccgtcc tcctgctgct ctcggcggcc ctggccctga 60
ccgagacctg ggccggctcc cactccatga ggtatttcga caccgccatg tcccggcccg 120
gccgcgggga gccccgcttc atctcagtgg gctacgtgga cgacacgcag ttcgtgaggt 180
tcgacagcga cgccgcgagt ccgagagagg agccgcgggc gccgtggata gagcaggagg 240
ggccggagta ttgggaccgg aacacacaga tcttcaagac caacacacag actgaccgag 300
agagcctgcg gaacctgcgc ggctactaca accagagcga ggccgggtct cacaccctcc 360
agagcatgta cggctgcgac gtggggccgg acgggcgcct cctccgcggg cataaccagt 420
acgcctacga cggcaaggat tacatcgccc tgaacgagga cctgcgct 468

<210> 134
<211> 214
<212> DNA
<213> Homo sapien

<400> 134
gaattcggca cgagctgcgt cctgctgagc tctgttctct ccagcacctc ccaacccact 60
agtgcctggt tctcttgctc caccaggaac aagccaccat gtctcgccag tcaagtgtgt 120
ccttccggag cgggggcagt cgtagcttca gcaccgcctc tgccatcacc ccgtctgtct 180
cccgcaccag cttcacctcc gtgtcccggt ccgg 214

<210> 135
<211> 355
<212> DNA
<213> Homo sapien

<400> 135
gaattcggca cgaggtgaac aggacccgtc gccatgggcc gtgtgatccg tggacagagg 60
aagggcgccg ggtctgtgtt ccgcgcgcac gtgaagcacc gtaaaggcgc tgcgcgcctg 120
cgcgccgtgg atttcgctga gcggcacggc tacatcaagg gcatcgtcaa ggacatcatc 180
cacgacccgg gccgcggcgc gcccctcgcc aaggtggtct tccgggatcc gtatcggttt 240
aagaagcgga cggagctgtt cattgccgcc gagggcattc acacgggcca gtttgtgtat 300
tgcggcaaga aggcccagct caacattggc aatgtgctcc ctgtgggcac catgc 355

<210> 136
<211> 242
<212> DNA
<213> Homo sapien

<400> 136
gaattcggca cgagccagct cctaaccgcg agtgatccgc cagcctccgc ctcccgaggt 60
gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc 120
agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca 180
aagtgccgag attgcagctc tctgcccggc cgccaccct gtctgggaag tgaggatgct 240
gt 242

<210> 137
<211> 424
<212> DNA
<213> Homo sapien

<400> 137
gaattcggca cgagcccaga tcccgaggtc cgacagcgcc cggcccagat ccccacgcct 60

gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc 120
ttcgacccga gccccgcgcc ctttccggga cccctgcccc gcgggcagcg ctgccaacct 180
gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
cactccgctg tcgcccaccc gcatcacccg gctgcaggag aaggaggacc tgcaggagct 300
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 360
gctgcgcctt cgcatcaccg agtctgaaga ggtggtcagc cgcgaggtgt ccggcatcaa 420
ggcc 424

<210> 138
<211> 448
<212> DNA
<213> Homo sapien

<400> 138
gaattcggca cgagcctgtg ttccaggagc cgaatcagaa atgtcatcct caggcacgcc 60
agacttacct gtcctactca ccgatttgaa gattcaatat actaagatct tcataaacaa 120
tgaatggcat gattcagtga gtggcaagaa atttcctgtc tttaatcctg caactgagga 180
ggagctctgc caggtagaag aaggagataa ggaggatgtt gacaaggcag tgaaggccgc 240
aagacaggct tttcagattg gatccccgtg gcgtactatg gatgcttccg agaggggcg 300
actattatac aagttggctg atttaatcga aagagatcgt ctgctgctgg ccgacaatgg 360
agtcaatgaa tggtggaaaa ctctattcca atgcatatct gaatgattta gcaggctgca 420
tcaaaacatt gcgctactgt gcaggttg 448

<210> 139
<211> 510
<212> DNA
<213> Homo sapien

<400> 139
gaattcggca cgaggttccg tgcagctcac ggagaagcga atggacaaag tcggcaagta 60
ccccaaggag ctgcgcaagt gctgcgagga cggcatgcgg gagaacccca tgaggttctc 120
gtgccagcgc cggacccgtt tcatctccct ggcgaggcgt gcaagaaggt cttcctggac 180
tgctgcaact acatcacaga gctgcggcgg cagcacgcgc gggccagcca cctggcctgc 240
caggagtaac ctggatgagg acatcattgc agaagagaac atcgtttccc gaagtgagtt 300
cccagagagc tggctgtgga acgttgagga cttgaaagag ccaccgaaaa atggaatctc 360
tacgaagctc atgaatatat ttttgaaaga ctccatcacc acgtgggaga ttctggctgt 420
gagcatgtcg gacaagaaag ggatctgtgt ggcagacccc ttcgaggtca cagtaatgca 480
ggacttcttc atcgacctgc ggctacccta 510

<210> 140
<211> 360
<212> DNA
<213> Homo sapien

<400> 140
gaattcggca cgagcggtaa ctaccccggc tgcgcacagc tcggcgctcc ttcccgctcc 60
ctcacacacc ggcctcagcc cgcaccggca gtagaagatg gtgaaagaaa caacttacta 120
cgatgttttg ggggtcaaac ccaatgctac tcaggaagaa ttgaaaaagg cttataggaa 180
actggctttg aagtaccatc ctgataagaa cccaaatgaa ggagagaagt ttaaacagat 240
ttctcaagct tacgaagttc tctctgatgc aaagaaaagg gaattatatg acaaaggagg 300
agaacaggca attaaagagg gtggagcagg tggcggtttt ggctccccca tggacatctt 360

<210> 141
<211> 483
<212> DNA
<213> Homo sapien

<400> 141

gaattcggca cgagagcaga ggctgatctt tgctggaaaa cagctggaag atgggctgca 60
ccctgtctga ctacaacatc cagaaagagt ccaccctgca cctggtgctc cgtctcagag 120
gtgggatgca aatcttcgtg aagacactca ctggcaagac catcaccctt gaggtggagc 180
ccagtgacac catcgagaac gtcaaagcaa agatccagga caaggaaggc attcctcctg 240
accagcagag gttgatcttt gccggaaagc agctggaaga tgggcgcacc ctgtctgact 300
acaacatcca gaaagagtct accctgcacc tggtgctccg tctcagaggt gggatgcaga 360
tcttcgtgaa gaccctgact ggtaagacca tcaccctcga ggtggagccc agtgacacca 420
tcgagaatgt caaggcaaag atccaagata aggaaggcat tcctcctgat cagcagaggt 480
tga 483

<210> 142
<211> 500
<212> DNA
<213> Homo sapien

<400> 142
gaattcggca cgaggcggcg acgaccgccg ggagcgtgtg cagcggcggc ggcggaagtg 60
gccggcgagc ccggtccccg ccggcaccat gcttcccttg tcactgctga agacggctca 120
gaatcacccc atgttggtgg agctgaaaaa tggggagacg tacaatggac acctggtgag 180
ctgcgacaac tggatgaaca ttaacctgcg agaagtcatc tgcacgtcca gggacgggga 240
caagttctgg cggatgcccg agtgctacat ccgcggcagc accatcaagt acctgcgcat 300
ccccgacgag atcatcgaca tggtcaagga ggaggtggtg gccaagggcc gcggccgcgg 360
aggcctgcag cagcagaagc agcagaaagg ccgcggcatg ggcggcgctg gccgaggtgt 420
gtttggtggc cggggccgag gtgggatccc gggcacaggc agaagccagc cagagaagaa 480
gcctggcaga caggcgggca 500

<210> 143
<211> 400
<212> DNA
<213> Homo sapien

<400> 143
gaattcggca cgagctcgga tgtcagcagg cgtcccaacc cagcaggaac tggctcaatt 60
ctcagaagaa agcgatcggc cccgaggcag gaaggccggc tccggtgcag ggcgcgccgc 120
ctgcgggctg cttcgggcca gggtcgaccc gagggccagc gcaagcagcg gcaacaggag 180
cgccaggagg acatgaggct ctgcctgcag tcagcaactt ggaatattca gacttcagac 240
cagcatcaca gattataacc ctccgtaaat catctgcatc ccagctccca tcaaaagcca 300
gcctgaagga cccatggaca cgtgactcca gtgttctcaa caacatctta gatcaagttg 360
gtttgcacaa catttgcatc tacttgggac aaagcaagaa 400

<210> 144
<211> 243
<212> DNA
<213> Homo sapien

<400> 144
gaattcggca cgagccagct cctaaccgcg agtgatccgc cagcctccgc ctcccgaggt 60
gcccggattg cagacggagt ctccttcact cagtgctcaa tggtgcccag gctggagtgc 120
agtggtgtga tctcggctcg ctacaacatc cacctcccag cagcctgcct tggcctccca 180
aagtgccgag attgcagcct ctgcccggcc gtcaccccgt ctgggaagtg aggagcgttt 240
ctg 243

<210> 145
<211> 450
<212> DNA
<213> Homo sapien

<400> 145

gaattcggca cgaggacagc aggaccgtgg aggccgcggc aggggtggca gtggtggcgg 60
cggcggcggc ggcggtggtg gttacaaccg cagcagtggt ggctatgaac ccagaggtcg 120
tggaggtggc cgtggaggca gaggtggcat gggcggaagt gaccgtggtg gcttcaataa 180
atttggtggc cctcgggacc aaggatcacg tcatgactcc gaacaggata attcagacaa 240
caacaccatc tttgtgcaag gcctgggtga gaatgttaca attgagtctg tggctgatta 300
cttcaagcag attggtatta ttaagacaaa caagaaaacg ggacagccca tgattaattt 360
gtacacagac agggaaactg gcaagctgaa gggagaggca acggtctctt ttgatgaccc 420
accttcagct aaagcagcct attgactggt 450

<210> 146
<211> 451
<212> DNA
<213> Homo sapien

<400> 146
gaattcggca cgagccatcg agtccctgcc tttcgacttg cagagaaatg tctcgctgat 60
gcgggagatc gacgcgaaat accaagagat cctgaaggag ctagacgagt gctacgagcg 120
cttcagtcgc gagacagacg gggcgcagaa gcggcggatg ctgcactgtg tgcagcgcgc 180
gctgatccgc accaggagct gggcgacgag aagatccaga tcgtgagcca gatggtggag 240
ctggtggaga accgcacgcg gcaggtggac agccacgtgg agctgttcga ggcgcagcag 300
gagctgggcg acacagcggg caacagcggc aaggctggcg cggacaggcc caaaggcgag 360
gcggcagcgc aggctgacaa gcccaacagc aagcgctcac ggcggcagcg caacaacgag 420
aaccgtgaga acgcgtccag caaccacgac c 451

<210> 147
<211> 400
<212> DNA
<213> Homo sapien

<400> 147
gaattcggca cgagctcgga tgtcagcagg cgtcccaacc cagcaggaac tggctcaatt 60
ctcagaagaa agcgatcggc cccgaggcag gaaggccggc tccggtgcag ggcgcgccgc 120
ctgcgggctg cttcgggcca gggtcgaccc gagggccagc gcaagcagcg gcaacaggag 180
cgccaggagg acatgaggct ctgcctgcag tcagcaactt ggaatattca gacttcagac 240
cagcatcaca gattataacc ctccgtaaat catctgcatc ccagctccca tcaaaagcca 300
gcctgaagga cccatggaca cgtgactcca gtgttctcaa caacatctta gatcaagttg 360
gtttgcacaa catttgcatc tacttgggac aaagcaagaa 400

<210> 148
<211> 503
<212> DNA
<213> Homo sapien

<400> 148
aaaagaattc ggcacgagcg gcgccgctca tccccctctc ccagcagatt cccactggaa 60
attcgttgta tgaatcttat tacaagcagg tcgatccggc atacacaggg agggtggggg 120
cgagtgaagc tgcgcttttt ctaaagaagt ctggcctctc ggacattatc cttgggaaga 180
tatgggactt ggccgatcca gaaggtaaag ggttcttgga caaacagggt ttctatgttg 240
cactgagact ggtggcctgt gcacagagtg gccatgaagt taccttgagc aatctgaatt 300
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<213> Homo sapien

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<213> Homo sapien

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<213> Homo sapien

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<210> 157
<211> 2313
<212> DNA
<213> Homo sapien

<400> 157
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<210> 158
<211> 2114
<212> DNA
<213> Homo sapien

<400> 158
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gagaataaca gaaatgtcca tttggagcac tcagagcaga atcctggttc atcagcaggt 120
gacacctcag cagcgcacca ggtggtttta ggagaaaact tgatagccac agccctttgt 180

ctttctggca gtgggtctca gtctgatttg aaggatgtgg ccagcacagc aggagaggag 240
ggggacacaa gccttcggga gagcctccat ccagtcactc ggtctcttaa ggcagggtgc 300
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ggggttgaag gagtccgagt ggatcaggat gatgatcaag atagctcttc cctgaagctt 480
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taccaggagg tcctggacaa acagaggcaa gtggagaatc agctccaagt gcaattaaag 660
cagcttcagc aaaggagaga agaggaaatg aagaatcacc aggagatatt aaaggctatt 720
caggatgtga caataaagcg ggaagaaaca aagaagaaga tagagaaaga gaagaaggag 780
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cgggagtact tcta 2114

<210> 159
<211> 278
<212> DNA
<213> Homo sapien

<400> 159
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tgcagaatga gaatcactcc taaaataggt aatggtaaaa attaaattga caattacctc 180
tctctatgca gaaggaaata tcacctatat gacatcatca tcatctattg atacttgctg 240
gcagtgctaa taatggtttt aatgccaatt tgtaagaa 278

<210> 160
<211> 848
<212> DNA
<213> Homo sapien

<400> 160
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gggaatcagg catgaagtca tcaatatcaa cctgaaaaat aagcctgagt ggttctttaa 240
gaaaaatccc tttggtctgg tgccagttct ggaaaacagt cagggtcagc tgatctacga 300
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atttcgtaaa gaatttacca agctagagga ggttctgact aataagaaga cgaccttctt 540
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catgaaggaa gatcccacag tctcagccct gcttactagt gagaaagact ggcaaggttt 720
cctagagctc tacttacaga acagccctga ggcctgtgac tatgggctct gaaggggca 780
ggagtcagca ataaagctat gtctgatatt ttccttcact aaaaaaaaaa aaaaaaaaaa 840
aactcgag 848

<210> 161
<211> 432
<212> DNA
<213> Homo sapien

<400> 161
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cttgagagag cgaggccggg agctgaccac tcagaggcag ctgatgcagg aacgggcaga 120
ggaagggaag ggcccaagta aagcacagcg cgggagccta gagcacatga agctgatcct 180
gcgtgataag gagaaggagg tggaatgtca gcaggagcat atccatgaac tccaggagct 240
caaagaccag ctggagcagc agctccaggg cctgcacagg aaggtaggtg agaccagcct 300
cctcctgtcc cagcgagagc aggaaatagt ggtcctgcag cagcaactgc aggaagccag 360
ggaacaaggg gagctgaagg agcagtcact tcagagtcaa ctggatgagg cccagagagc 420
cctagcccag ag 432

<210> 162
<211> 433
<212> DNA
<213> Homo sapien

<400> 162
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ttcaagctgg gagagggctc tagtccctgg ttctgaacac tctggggttc tcgggtgcag 120
gccgccatga gcaaacggaa ggcgccgcag gagactctca acgggggaat caccgacatg 180
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gctaagaaat tgcctggagt aggaacaaaa attgctgaaa agattgatga gtttttagca 360
actggaaaat tacgtaaact ggaaaagatt cggcaggatg atacgagttc atccatcaat 420
ttcctgactc gag 433

<210> 163
<211> 432
<212> DNA
<213> Homo sapien

<400> 163
gaattcggca ccagatgagg ccaacgaggt gacggacagc gcgtacatgg gctccgagag 60
cacctacagt gagtgtgaga ccttcacgga cgaggacacc agcaccctgg tgcaccctga 120
gctgcaacct gaaggggacg cagacagtgc cggcggctcg gccgtgccct ctgagtgcct 180
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ccccgctttc ctcacgccca gtccgacaaa gcggctctcc agcaagaagg tggcaaggta 420
cctgcaccag tc 432

<210> 164
<211> 395
<212> DNA

<213> Homo sapien

<400> 164
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gaggttcagg tggaaggtta taattacact ggcatgggaa attccaccaa taaaaaagat 180
gcacaaagca atgctgccag agactttgtt aactatttgg ttcgaataaa tgaaataaag 240
agtgaagaag ttccagcttt tggggtagca tctccgcccc cacttactga tactcctgac 300
actacagcaa atgctgaagg catcttgttg acatcgaata tgactttgat aataaatacc 360
ggttcctgaa aaaaaaaaaa aaaaaaaaac tcgag 395

<210> 165
<211> 503
<212> DNA
<213> Homo sapien

<400> 165
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acagctcggc gctccttccc gctccctcac acaccggcct cagcccgcac cggcagtaga 120
agatggtgaa agaaacaact tactacgatg ttttgggggt caaacccaat gctactcagg 180
aagaattgaa aaaggcttat aggaaactgg ccttgaagta ccatcctgat aagaacccaa 240
atgaaggaga gaagtttaaa cagatttctc aagcttacga agttctctct gatgcaaaga 300
aaagggaatt atatgacaaa ggaggagaac aggcaattaa agagggtgga gcaggtggcg 360
gttttggctc ccccatggac atctttgata tgtttttttgg aggaggagga aggatgcaga 420
gagaaaggag aggtaaaaat gttgtacatc agctctcagt aaccctagaa gacttatata 480
atggtgcaac aagaaaactg gct 503

<210> 166
<211> 893
<212> DNA
<213> Homo sapien

<400> 166
gaattcggca cgagaggaac ttctcttgac gagaagagag accaaggagg ccaagcaggg 60
gctgggccag aggtgccaac atggggaaac tgaggctcgg ctcggaaggg tgagagtgag 120
actacatctc aaaaaaaaaa aaaaaaaaaa aaaagaaaga aaagaaaaga aaaaagaaag 180
aacggaagta gttgtaggta gtggtatggt ggtatgagtc tgttttctgt tacttataac 240
aacaacaaca acaaaaaacg ctgaaactgg gtaatttata aagaaaagga aaaaaagcag 300
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gtggagactc tttgtggagt cctgggacag tgcagaagga tcacgcctcc ctaccgctcc 480
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ccttcctggg ggccttggct ttgatctaca atgaagccct caagggctga aaataaatag 780
ggaagatgga gacaccctct gggggtcctc tctgagtcaa atccagtggt gggtaattgt 840
acaataaatt ttttttggtc aaatttaaaa aaaaaaaaaa aaaaaactc gag 893

<210> 167
<211> 549
<212> DNA
<213> Homo sapien

<400> 167
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gccaggagca agccgagagc cagccggccg gcgcactccg actccgagca gtctctgtcc 120
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gccggccatg gagaccccgt cccagcggcg cgccacccgc agcggggcgc aggccagctc 240
cactccgctg tcgcccaccc gcatcacccg gctgcaggag aaggaggacc tgcaggagct 300
caatgatcgc ttggcggtct acatcgaccg tgtgcgctcg ctggaaacgg agaacgcagg 360
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ggccgcctac gaggccgagc tcggggatgc ccgcaagacc cttgactcag tagccaagga 480
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gcgcaatac 549

<210> 168
<211> 547
<212> DNA
<213> Homo sapien

<400> 168
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tcaaaatgga ggaagagagc ggcgcgcccg gcgtgccgag cggcaacggg gctccgggcc 120
ctaagggtga aggagaacga cctgctcaga atgagaagag gaaggagaaa aacataaaaa 180
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caaacatacc ttttgatgtg aaatggcagt cacttaaaga cctggttaaa gaaaaagttg 300
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ttggctg 547

<210> 169
<211> 547
<212> DNA
<213> Homo sapien

<400> 169
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gatagtggct tccagatgaa ccagcttcga ggcaagaagt cctgccacac gggtctaggc 480
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aaacctc 547

<210> 170
<211> 838
<212> DNA
<213> Homo sapien

<400> 170
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gagcttgggg aagggaagcg cgcccccggg gccggtcccg gagggctcga tccgcatcta 120
cagcatgagg ttctgcccgt ttgctgagag gacgcgtcta gtcctgaagg ccaagggaat 180
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gaagttaaat gagtgtgtag accacactcc aaaactgaaa ctgtggatgg cagccatgaa 660
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gctctactta cagaacagcc ctgaggcctg tgactatggg ctctgaaggg ggcaggagtc 780
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<210> 171
<211> 547
<212> DNA
<213> Homo sapien

<400> 171
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gcccagtgac accatcgaga atgtcaaggc aaagatccaa gataaggaag gcatccctcc 180
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aatcttcgtg aagacactca ctggcaagac catcaccctt gaggtcgagc ccagtgacac 360
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gaaagagtct accctgcacc tggtgctccg tctcagaggt gggatgcaga tcttcgtgaa 540
gaccctg 547

<210> 172
<211> 608
<212> DNA
<213> Homo sapien

<400> 172
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caccctcatc tacaatggtg ccctgccatg tcagtgcaac cctcaaggtt cactgagttc 120
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ggacccacgg ctgccatatg ggggccagtg ccggccctgt ccctgtcctg aaggccctgg 360
gagccaacgg cactttgcta cttcttgcca ccaggatgaa tattcccagc agattgtgtg 420
ccactgccgg gcaggctata cggggctgcg atgtgaagct tgtgcccctg ggcactttgg 480
ggacccatca aggccaggtg gccggtgcca actgtgtgag tgcagtggga acattgaccc 540
aatggatcct gatgcctgtg acccccacac ggggcaatgc ctgcgctgtt tacaccacac 600
agagggtc 608

<210> 173
<211> 543
<212> DNA
<213> Homo sapien

<400> 173
gaattcggca ccagagatca tccgccagca gggtctggcc tcctacgact acgtgcgccg 60
ccgcctcacg gctgaggacc tgttcgaggc tcggatcatc tctctcgaga cctacaacct 120
gctccgggag ggcaccagga gcctccgtga ggctctcgag gcggagtccg cctggtgcta 180
cctctatggc acgggctccg tggctggtgt ctacctgccc ggttccaggc agacactgag 240
catctaccag gctctcaaga aagggctgct gagtgccgag gtggcccgcc tgctgctgga 300
ggcacaggca gccacaggct tcctgctgga cccggtgaag ggggaacggc tgactgtgga 360
tgaagctgtg cggaagggcc tcgtggggcc cgaactgcac gaccgcctgc tctcggctga 420
gcgggcggtc accggctacc gtgaccccta caccgagcag accatctcgc tcttccaggc 480
catgaagaag gaactgatcc ctactgagga ggccctgcgg ctgtggatgc ccagctggcc 540
acc 543

<210> 174

<211> 548
<212> DNA
<213> Homo sapien

<400> 174
gaattcggca cgagaaatgg cggcaggggt cgaagcggcg gcggaggtgg cggcgacgga 60
gatcaaaatg gaggaagaga gcggcgcgcc cggcgtgccg agcggcaacg gggctccggg 120
ccctaagggt gaaggagaac gacctgctca gaatgagaag aggaaggaga aaaacataaa 180
aagaggaggc aatcgctttg agccatatgc caatccaact aaaagataca gagccttcat 240
tacaaacata ccttttgatg tgaaatggca gtcacttaaa gacctggtta aagaaaaagt 300
tggtgaggta acatacgtgg agctcttaat ggacgctgaa ggaaagtcaa ggggatgtgc 360
tgttgttgaa ttcaagatgg aagagagcat gaaaaaagct gcggaagtcc taaacaagca 420
tagtctgagc ggaagaccac tgaaagtcaa agaagatcct gatggtgaac atgccaggag 480
agcaatgcaa aaggtgatgg ctacgactgg tgggatgggt atgggaccag gtggcccagg 540
aatgatta 548

<210> 175
<211> 604
<212> DNA
<213> Homo sapien

<400> 175
gaattcggca ccagaggacc tccaggacat gttcatcgtc cataccatcg aggagattga 60
gggcctgatc tcagcccatg accagttcaa gtccaccctg ccggacgccg atagggagcg 120
cgaggccatc ctggccatcc acaaggaggc ccagaggatc gctgagagca accacatcaa 180
gctgtcgggc agcaacccct acaccaccgt caccccgcaa atcatcaact ccaagtggga 240
gaaggtgcag cagctggtgc caaaacggga ccatgccctc ctggaggagc agagcaagca 300
gcagtccaac gagcacctgc gccgccagtt cgccagccag gccaatgttg tggggccctg 360
gatccagacc aagatggagg agatcgggcg catctccatt gagatgaacg ggaccctgga 420
ggaccagctg agccacctga agcagtatga acgcagcatc gtggactaca agcccaacct 480
ggacctgctg gagcagcagc accagcttat ccaggaggcc ctcatcttcg acaacaagca 540
caccaactat accatggagc acatccgcgt gggctgggag cagctgctca ccaccattgc 600
ccgg 604

<210> 176
<211> 486
<212> DNA
<213> Homo sapien

<400> 176
gaattcggca ccagccaagc tcactattga atccacgccg ttcaatgtcg cagaggggaa 60
ggaggttctt ctactcgccc acaacctgcc ccagaatcgt attggttaca gctggtacaa 120
aggcgaaaga gtggatggca acagtctaat tgtaggatat gtaataggaa ctcaacaagc 180
taccccaggg cccgcataca gtggtcgaga gacaatatac cccaatgcat ccctgctgat 240
ccagaacgtc acccagaatg acacaggatt ctatacccta caagtcataa agtcagatct 300
tgtgaatgaa gaagcaaccg gacagttcca tgtatacccg gagctgccca agccctccat 360
ctccagcaac aactccaacc ccgtggagga caaggatgct gtggccttca cctgtgaacc 420
tgaggttcag aacacaacct acctgtggtg ggtaaatggt cagagcctcc cggtcagtcc 480
caaggc 486

<210> 177
<211> 387
<212> DNA
<213> Homo sapien

<400> 177
gaattcggca ccagggacag cagaccagac agtcacagca gccttgacaa aacgttcctg 60
gaactcaagc tcttctccac agaggaggac agagcagaca gcagagacca tggagtctcc 120

ctcggcccct ccccacagat ggtgcatccc ctggcagagg ctcctgctca cagcctcact 180
tctaaccttc tggaacccgc ccaccactgc caagctcact attgaatcca cgccgttcaa 240
tgtcgcagag gggaaggagg tgcttctact tgtccacaat ctgccccagc atcttttgg 300
ctacagctgg tacaaaggtg aaagagtgga tggcaaccgt caaattatag gatatgtaat 360
aggaactcaa caagctaccc cagggcc 387

<210> 178
<211> 440
<212> DNA
<213> Homo sapien

<400> 178
gaattcggca cgaggagaag cagaaaaaca aggaatttag ccagacttta gaaaatgaga 60
aaaatacctt actgagtcag atatcaacaa aggatggtga actaaaaatg cttcaggagg 120
aagtaaccaa aatgaacctg ttaaatcagc aaatccaaga agaactctct agagttacca 180
aactaaagga gacagcagaa gaagagaaag atgatttgga agagaggctt atgaatcaat 240
tagcagaact taatggaagc attgggaatt actgtcagga tgttacagat gcccaaataa 300
aaaatgagct attggaatct gaaatgaaga accttaaaaa gtgtgtgagt gaattggaag 360
aagaaaagca gcagttagtc aaggaaaaaa ctaaggtgga atcagaaata cgaaaggaat 420
atttggagaa aatacaaggt 440

<210> 179
<211> 443
<212> DNA
<213> Homo sapien

<400> 179
gaattcggca ccagcggggg gctacggcgg cggctacggc ggcgtcctga ccgcgtccga 60
cgggctgctg gcgggcaacg agaagctaac catgcagaac ctcaacgacc gcctggcctc 120
ctacctggac aaggtgcgcg ccctggaggc ggccaacggc gagctagagg tgaagatccg 180
cgactggtac cagaagcagg ggcctgggcc ctcccgcgac tacagccact actacacgac 240
catccaggac ctgcgggaca agattcttgg tgccaccatt gagaactcca ggattgtcct 300
gcagatcgac aacgcccgtc tggctgcaga tgacttccga accaagtttg agacggaaca 360
ggctctgcgc atgagcgtgg aggccgacat caacggcctg cgcagggtgc tggatgagct 420
gaccctggcc aggaccgacc tgg 443

<210> 180
<211> 403
<212> DNA
<213> Homo sapien

<400> 180
gaattcggca cgaggttatg agagtcgact tcaatgttcc tatgaagaac aaccagataa 60
caaacaacca gaggattaag gctgctgtcc caagcatcaa attctgcttg gacaatggag 120
ccaagtcggt agtccttatg agccacctag gccggcctga tggtgtgccc atgcctgaca 180
agtactcctt agagccagtt gctgtagaac tcagatctct gctgggcaag gatgttctgt 240
tcttgaagga ctgtgtaggc ccagaagtgg agaaagcctg tgccaaccca gctgctgggt 300
ctgtcatcct gctggagaac ctccgctttc atgtggagga agaagggaag ggaaaagatg 360
cttctgggaa caaggttaaa gccgagccag ccaaaataga agc 403

<210> 181
<211> 493
<212> DNA
<213> Homo sapien

<400> 181
gaattcggca ccagcagagg tctccagagc cttctctctc ctgtgcaaaa tggcaactct 60
taaggaaaaa ctcattgcac cagttgcgga agaagaggca acagttccaa acaataagat 120

cactgtagtg ggtgttggac aagttggtat ggcgtgtgct atcagcattc tgggaaagtc 180
tctggctgat gaacttgctc ttgtggatgt tttggaagat aagcttaaag gagaaatgat 240
ggatctgcag catgggagct tatttcttca gacacctaaa attgtggcag ataaagatta 300
ttctgtgacc gccaattcta agattgtagt ggtaactgca ggagtccgtc agcaagaagg 360
ggagagtcgg ctcaatctgg tgcagagaaa tgttaatgtc ttcaaattca ttattcctca 420
gatcgtcaag tacagtcctg attgcatcat aattgtggtt tccaacccag tggacattct 480
tacgtatgtt acc 493

<210> 182
<211> 209
<212> PRT
<213> Homo sapien

<400> 182

```
Ala Phe Ser Ser Asn Pro Lys Val Gln Val Glu Ala Ile Glu Gly Gly
 1               5                  10                  15
Ala Leu Gln Lys Leu Leu Val Ile Leu Ala Thr Glu Gln Pro Leu Thr
            20                  25                  30
Ala Lys Lys Lys Val Leu Phe Ala Leu Cys Ser Leu Leu Arg His Phe
        35                  40                  45
Pro Tyr Ala Gln Arg Gln Phe Leu Lys Leu Gly Gly Leu Gln Val Leu
    50                  55                  60
Arg Thr Leu Val Gln Glu Lys Gly Thr Glu Val Leu Ala Val Arg Val
65                  70                  75                  80
Val Thr Leu Leu Tyr Asp Leu Val Thr Glu Lys Met Phe Ala Glu Glu
                85                  90                  95
Glu Ala Glu Leu Thr Gln Glu Met Ser Pro Glu Lys Leu Gln Gln Tyr
            100                 105                 110
Arg Gln Val His Leu Leu Pro Gly Leu Trp Glu Gln Gly Trp Cys Glu
        115                 120                 125
Ile Thr Ala His Leu Leu Ala Leu Pro Glu His Asp Ala Arg Glu Lys
    130                 135                 140
Val Leu Gln Thr Leu Gly Val Leu Leu Thr Thr Cys Arg Asp Arg Tyr
145                 150                 155                 160
Arg Gln Asp Pro Gln Leu Gly Arg Thr Leu Ala Ser Leu Gln Ala Glu
                165                 170                 175
Tyr Gln Val Leu Ala Ser Leu Glu Leu Gln Asp Gly Glu Asp Glu Gly
            180                 185                 190
Tyr Phe Gln Glu Leu Leu Gly Ser Val Asn Ser Leu Leu Lys Glu Leu
        195                 200                 205
Arg
```

<210> 183
<211> 255
<212> PRT
<213> Homo sapien

<400> 183

```
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Pro
 1               5                  10                  15
Lys Met Glu Glu Glu Ser Gly Ala Pro Cys Val Pro Ser Gly Asn Gly
            20                  25                  30
Ala Pro Gly Pro Lys Gly Glu Glu Arg Pro Thr Gln Asn Glu Lys Arg
        35                  40                  45
Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr Ser
    50                  55                  60
Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe Asp
```

65 70 75 80
Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly Glu
85 90 95
Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg Gly
100 105 110
Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala Ala
115 120 125
Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val Lys
130 135 140
Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala Gly
145 150 155 160
Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val Gly
165 170 175
Trp Lys Lys Leu Lys Glu Val Phe Ser Met Ala Gly Val Val Val Arg
180 185 190
Ala Asp Ile Leu Glu Asp Lys Asp Gly Lys Ser Arg Gly Ile Gly Ile
195 200 205
Val Thr Phe Glu Gln Ser Ile Glu Ala Val Gln Ala Ile Ser Met Phe
210 215 220
Asn Gly Gln Leu Leu Phe Asp Arg Pro Met His Val Lys Met Asp Glu
225 230 235 240
Arg Ala Leu Pro Lys Gly Asp Phe Phe Pro Pro Glu Arg His Ser
245 250 255

<210> 184
<211> 188
<212> PRT
<213> Homo sapien

<400> 184
Leu Ser Gly Ser Cys Ile Arg Arg Glu Gln Thr Pro Glu Lys Glu Lys
1 5 10 15
Gln Val Val Leu Phe Glu Glu Ala Ser Trp Thr Cys Thr Pro Ala Cys
20 25 30
Gly Asp Glu Pro Arg Thr Val Ile Leu Leu Ser Ser Met Leu Ala Asp
35 40 45
His Arg Leu Lys Leu Glu Asp Tyr Lys Asp Arg Leu Lys Ser Gly Glu
50 55 60
His Leu Asn Pro Asp Gln Leu Glu Ala Val Glu Lys Tyr Glu Glu Val
65 70 75 80
Leu His Asn Leu Glu Phe Ala Lys Glu Leu Gln Lys Thr Phe Ser Gly
85 90 95
Leu Ser Leu Asp Leu Leu Lys Ala Gln Lys Lys Ala Gln Arg Arg Glu
100 105 110
His Met Leu Lys Leu Glu Ala Glu Lys Lys Lys Leu Arg Thr Ile Leu
115 120 125
Gln Val Gln Tyr Val Leu Gln Asn Leu Thr Gln Glu His Val Gln Lys
130 135 140
Asp Phe Lys Gly Gly Leu Asn Gly Ala Val Tyr Leu Pro Ser Lys Glu
145 150 155 160
Leu Asp Tyr Leu Ile Lys Phe Ser Lys Leu Thr Cys Pro Glu Arg Asn
165 170 175
Glu Ser Leu Arg Gln Thr Leu Glu Gly Ser Thr Val
180 185

<210> 185
<211> 746
<212> PRT

<213> Homo sapien

<400> 185

```
Asp Lys His Leu Lys Asp Leu Leu Ser Lys Leu Leu Asn Ser Gly Tyr
 1               5                  10                  15
Phe Glu Ser Ile Pro Val Pro Lys Asn Ala Lys Glu Lys Glu Val Pro
            20                  25                  30
Leu Glu Glu Glu Met Leu Ile Gln Ser Glu Lys Lys Thr Gln Leu Ser
        35                  40                  45
Lys Thr Glu Ser Val Lys Glu Ser Glu Ser Leu Met Glu Phe Ala Gln
    50                  55                  60
Pro Glu Ile Gln Pro Gln Glu Phe Leu Asn Arg Arg Tyr Met Thr Glu
65                  70                  75                  80
Val Asp Tyr Ser Asn Lys Gln Gly Glu Glu Gln Pro Trp Glu Ala Asp
                85                  90                  95
Tyr Ala Arg Lys Pro Asn Leu Pro Lys Arg Trp Asp Met Leu Thr Glu
            100                 105                 110
Pro Asp Gly Gln Glu Lys Lys Gln Glu Ser Phe Lys Ser Trp Glu Ala
        115                 120                 125
Ser Gly Lys His Gln Glu Val Ser Lys Pro Ala Val Ser Leu Glu Gln
    130                 135                 140
Arg Lys Gln Asp Thr Ser Lys Leu Arg Ser Thr Leu Pro Glu Glu Gln
145                 150                 155                 160
Lys Lys Gln Glu Ile Ser Lys Ser Lys Pro Ser Pro Ser Gln Trp Lys
                165                 170                 175
Gln Asp Thr Pro Lys Ser Lys Ala Gly Tyr Val Gln Glu Glu Gln Lys
            180                 185                 190
Lys Gln Glu Thr Pro Lys Leu Trp Pro Val Gln Leu Gln Lys Glu Gln
        195                 200                 205
Asp Pro Lys Lys Gln Thr Pro Lys Ser Trp Thr Pro Ser Met Gln Ser
    210                 215                 220
Glu Gln Asn Thr Thr Lys Ser Trp Thr Thr Pro Met Cys Glu Glu Gln
225                 230                 235                 240
Asp Ser Lys Gln Pro Glu Thr Pro Lys Ser Trp Glu Asn Asn Val Glu
                245                 250                 255
Ser Gln Lys His Ser Leu Thr Ser Gln Ser Gln Ile Ser Pro Lys Ser
            260                 265                 270
Trp Gly Val Ala Thr Ala Ser Leu Ile Pro Asn Asp Gln Leu Leu Pro
        275                 280                 285
Arg Lys Leu Asn Thr Glu Pro Lys Asp Val Pro Lys Pro Val His Gln
    290                 295                 300
Pro Val Gly Ser Ser Ser Thr Leu Pro Lys Asp Pro Val Leu Arg Lys
305                 310                 315                 320
Glu Lys Leu Gln Asp Leu Met Thr Gln Ile Gln Gly Thr Cys Asn Phe
                325                 330                 335
Met Gln Glu Ser Val Leu Asp Phe Asp Lys Pro Ser Ser Ala Ile Pro
            340                 345                 350
Thr Ser Gln Pro Pro Ser Ala Thr Pro Gly Ser Pro Val Ala Ser Lys
        355                 360                 365
Glu Gln Asn Leu Ser Ser Gln Ser Asp Phe Leu Gln Glu Pro Leu Gln
    370                 375                 380
Val Phe Asn Val Asn Ala Pro Leu Pro Pro Arg Lys Glu Gln Glu Ile
385                 390                 395                 400
Lys Glu Ser Pro Tyr Ser Pro Gly Tyr Asn Gln Ser Phe Thr Thr Ala
                405                 410                 415
Ser Thr Gln Thr Pro Pro Gln Cys Gln Leu Pro Ser Ile His Val Glu
            420                 425                 430
Gln Thr Val His Ser Gln Glu Thr Ala Ala Asn Tyr His Pro Asp Gly
```

```
        435                 440                 445
Thr Ile Gln Val Ser Asn Gly Ser Leu Ala Phe Tyr Pro Ala Gln Thr
    450                 455                 460
Asn Val Phe Pro Arg Pro Thr Gln Pro Phe Val Asn Ser Arg Gly Ser
465                 470                 475                 480
Val Arg Gly Cys Thr Arg Gly Gly Arg Leu Ile Thr Asn Ser Tyr Arg
                485                 490                 495
Ser Pro Gly Gly Tyr Lys Gly Phe Asp Thr Tyr Arg Gly Leu Pro Ser
            500                 505                 510
Ile Ser Asn Gly Asn Tyr Ser Gln Leu Gln Phe Gln Ala Arg Glu Tyr
        515                 520                 525
Ser Gly Ala Pro Tyr Ser Gln Arg Asp Asn Phe Gln Gln Cys Tyr Lys
    530                 535                 540
Arg Gly Gly Thr Ser Gly Gly Pro Arg Ala Asn Ser Arg Ala Gly Trp
545                 550                 555                 560
Ser Asp Ser Ser Gln Val Ser Ser Pro Glu Arg Asp Asn Glu Thr Phe
                565                 570                 575
Asn Ser Gly Asp Ser Gly Gln Gly Asp Ser Arg Ser Met Thr Pro Val
            580                 585                 590
Asp Val Pro Val Thr Asn Pro Ala Ala Thr Ile Leu Pro Val His Val
        595                 600                 605
Tyr Pro Leu Pro Gln Gln Met Arg Val Ala Phe Ser Ala Ala Arg Thr
    610                 615                 620
Ser Asn Leu Ala Pro Gly Thr Leu Asp Gln Pro Ile Val Phe Asp Leu
625                 630                 635                 640
Leu Leu Asn Asn Leu Gly Glu Thr Phe Asp Leu Gln Leu Gly Arg Phe
                645                 650                 655
Asn Cys Pro Val Asn Gly Thr Tyr Val Phe Ile Phe His Met Leu Lys
            660                 665                 670
Leu Ala Val Asn Val Pro Leu Tyr Val Asn Leu Met Lys Asn Glu Glu
        675                 680                 685
Val Leu Val Ser Ala Tyr Ala Asn Asp Gly Ala Pro Asp His Glu Thr
    690                 695                 700
Ala Ser Asn His Ala Ile Leu Gln Leu Phe Gln Gly Asp Gln Ile Trp
705                 710                 715                 720
Leu Arg Leu His Arg Gly Ala Ile Tyr Gly Ser Ser Trp Lys Tyr Ser
                725                 730                 735
Thr Phe Ser Gly Tyr Leu Leu Tyr Gln Asp
            740                 745
```

<210> 186
<211> 705
<212> PRT
<213> Homo sapien

<400> 186

```
Ala Leu Leu Asn Val Arg Gln Pro Pro Ser Thr Thr Thr Phe Val Leu
 1               5                  10                  15
Asn Gln Ile Asn His Leu Pro Pro Leu Gly Ser Thr Ile Val Met Thr
            20                  25                  30
Lys Thr Pro Pro Val Thr Thr Asn Arg Gln Thr Ile Thr Leu Thr Lys
        35                  40                  45
Phe Ile Gln Thr Thr Ala Ser Thr Arg Pro Ser Val Ser Ala Pro Thr
    50                  55                  60
Val Arg Asn Ala Met Thr Ser Ala Pro Ser Lys Asp Gln Val Gln Leu
65                  70                  75                  80
Lys Asp Leu Leu Lys Asn Asn Ser Leu Asn Glu Leu Met Lys Leu Lys
                85                  90                  95
```

```
Pro Pro Ala Asn Ile Ala Gln Pro Val Ala Thr Ala Ala Thr Asp Val
            100                 105                 110
Ser Asn Gly Thr Val Lys Lys Glu Ser Ser Asn Lys Glu Gly Ala Arg
        115                 120                 125
Met Trp Ile Asn Asp Met Lys Met Arg Ser Phe Ser Pro Thr Met Lys
    130                 135                 140
Val Pro Val Val Lys Glu Asp Asp Glu Pro Glu Glu Glu Asp Glu Glu
145                 150                 155                 160
Glu Met Gly His Ala Glu Thr Tyr Ala Glu Tyr Met Pro Ile Lys Leu
                165                 170                 175
Lys Ile Gly Leu Arg His Pro Asp Ala Val Val Glu Thr Ser Ser Leu
            180                 185                 190
Ser Ser Val Thr Pro Pro Asp Val Trp Tyr Lys Thr Ser Ile Ser Glu
        195                 200                 205
Glu Thr Ile Asp Asn Gly Trp Leu Ser Ala Leu Gln Leu Glu Ala Ile
    210                 215                 220
Thr Tyr Ala Ala Gln Gln His Glu Thr Phe Leu Pro Asn Gly Asp Arg
225                 230                 235                 240
Ala Gly Phe Leu Ile Gly Asp Gly Ala Gly Val Gly Lys Gly Arg Thr
                245                 250                 255
Ile Ala Gly Ile Ile Tyr Glu Asn Tyr Leu Leu Ser Arg Lys Arg Ala
            260                 265                 270
Leu Trp Phe Ser Val Ser Asn Asp Leu Lys Tyr Asp Ala Glu Arg Asp
        275                 280                 285
Leu Arg Asp Ile Gly Ala Lys Asn Ile Leu Val His Ser Leu Asn Lys
    290                 295                 300
Phe Lys Tyr Gly Lys Ile Ser Ser Lys His Asn Gly Ser Val Lys Lys
305                 310                 315                 320
Gly Val Ile Phe Ala Thr Tyr Ser Ser Leu Ile Gly Glu Ser Gln Ser
                325                 330                 335
Gly Gly Lys Tyr Lys Thr Arg Leu Lys Gln Leu Leu His Trp Cys Gly
            340                 345                 350
Asp Asp Phe Asp Gly Val Ile Val Phe Asp Glu Cys His Lys Ala Lys
        355                 360                 365
Asn Leu Cys Pro Val Gly Ser Ser Lys Pro Thr Lys Thr Gly Leu Ala
    370                 375                 380
Val Leu Glu Leu Gln Asn Lys Leu Pro Lys Ala Arg Val Val Tyr Ala
385                 390                 395                 400
Ser Ala Thr Gly Ala Ser Glu Pro Arg Asn Met Ala Tyr Met Asn Arg
                405                 410                 415
Leu Gly Ile Trp Gly Glu Gly Thr Pro Phe Arg Glu Phe Ser Asp Phe
            420                 425                 430
Ile Gln Ala Val Glu Arg Arg Gly Val Gly Ala Met Glu Ile Val Ala
        435                 440                 445
Met Asp Met Lys Leu Arg Gly Met Tyr Ile Ala Arg Gln Leu Ser Phe
    450                 455                 460
Thr Gly Val Thr Phe Lys Ile Glu Glu Val Leu Leu Ser Gln Ser Tyr
465                 470                 475                 480
Val Lys Met Tyr Asn Lys Ala Val Lys Leu Trp Val Ile Ala Arg Glu
                485                 490                 495
Arg Phe Gln Gln Ala Ala Asp Leu Ile Asp Ala Glu Gln Arg Met Lys
            500                 505                 510
Lys Ser Met Trp Gly Gln Phe Trp Ser Ala His Gln Arg Phe Phe Lys
        515                 520                 525
Tyr Leu Cys Ile Ala Ser Lys Val Lys Arg Val Val Gln Leu Ala Arg
    530                 535                 540
Glu Glu Ile Lys Asn Gly Lys Cys Val Val Ile Gly Leu Gln Ser Thr
545                 550                 555                 560
```

```
Gly Glu Ala Arg Thr Leu Glu Ala Leu Glu Glu Gly Gly Gly Glu Leu
                565                 570                 575
Asn Asp Phe Val Ser Thr Ala Lys Gly Val Leu Gln Ser Leu Ile Glu
            580                 585                 590
Lys His Phe Pro Ala Pro Asp Arg Lys Lys Leu Tyr Ser Leu Leu Gly
        595                 600                 605
Ile Asp Leu Thr Ala Pro Ser Asn Asn Ser Ser Pro Arg Asp Ser Pro
    610                 615                 620
Cys Lys Glu Asn Lys Ile Lys Lys Arg Lys Gly Glu Glu Ile Thr Arg
625                 630                 635                 640
Glu Ala Lys Lys Ala Arg Lys Val Gly Gly Leu Thr Gly Ser Ser Ser
                645                 650                 655
Asp Asp Ser Gly Ser Glu Ser Asp Ala Ser Asp Asn Glu Glu Ser Asp
            660                 665                 670
Tyr Glu Ser Ser Lys Asn Met Ser Ser Gly Asp Asp Asp Asp Phe Asn
        675                 680                 685
Pro Phe Leu Asp Glu Ser Asn Glu Asp Asp Glu Asn Asp Pro Trp Leu
    690                 695                 700
Ile
705
```

<210> 187
<211> 595
<212> PRT
<213> Homo sapien

<400> 187

```
Glu Ser Pro Arg His Arg Gly Glu Gly Gly Gly Glu Trp Gly Pro Gly
 1               5                  10                  15
Val Pro Arg Glu Arg Arg Glu Ser Ala Gly Glu Trp Gly Ala Asp Thr
            20                  25                  30
Pro Lys Glu Gly Gly Glu Ser Ala Gly Glu Trp Gly Ala Glu Val Pro
        35                  40                  45
Arg Gly Arg Gly Glu Gly Ala Gly Glu Trp Gly Pro Asp Thr Pro Lys
    50                  55                  60
Glu Arg Gly Gln Gly Val Arg Glu Trp Gly Pro Glu Ile Pro Gln Glu
65                  70                  75                  80
His Gly Glu Ala Thr Arg Asp Trp Ala Leu Glu Ser Pro Arg Ala Leu
                85                  90                  95
Gly Glu Asp Ala Arg Glu Leu Gly Ser Ser Pro His Asp Arg Gly Ala
            100                 105                 110
Ser Pro Arg Asp Leu Ser Gly Glu Ser Pro Cys Thr Gln Arg Ser Gly
        115                 120                 125
Leu Leu Pro Glu Arg Arg Gly Asp Ser Pro Trp Pro Pro Trp Pro Ser
    130                 135                 140
Pro Gln Glu Arg Asp Ala Gly Thr Arg Asp Arg Glu Glu Ser Pro Arg
145                 150                 155                 160
Asp Trp Gly Gly Ala Glu Ser Pro Arg Gly Trp Glu Ala Gly Pro Arg
                165                 170                 175
Glu Trp Gly Pro Ser Pro Ser Gly His Gly Asp Gly Pro Arg Arg Arg
            180                 185                 190
Pro Arg Lys Arg Arg Gly Arg Lys Gly Arg Met Gly Arg Gln His Glu
        195                 200                 205
Ala Ala Ala Thr Ala Ala Thr Ala Ala Thr Ala Thr Gly Gly Thr Ala
    210                 215                 220
Glu Glu Ala Gly Ala Ser Ala Pro Glu Ser Gln Ala Gly Gly Gly Pro
225                 230                 235                 240
Arg Gly Arg Ala Arg Gly Pro Arg Gln Gln Gly Arg Arg Arg His Gly
```

```
                245                 250                 255
Thr Gln Arg Arg Arg Gly Pro Pro Gln Ala Arg Glu Glu Gly Pro Arg
            260                 265                 270
Asp Ala Thr Thr Ile Leu Gly Leu Gly Thr Pro Ser Gly Glu Gln Arg
        275                 280                 285
Ala Asp Gln Ser Gln Ala Leu Pro Ala Leu Ala Gly Ala Ala Ala Ala
    290                 295                 300
His Ala His Ala Ile Pro Gly Ala Gly Pro Ala Ala Ala Pro Val Gly
305                 310                 315                 320
Gly Arg Gly Arg Arg Gly Gly Trp Arg Gly Gly Arg Arg Gly Gly Ser
                325                 330                 335
Ala Gly Ala Gly Gly Gly Gly Arg Gly Gly Arg Gly Arg Gly Arg Gly
            340                 345                 350
Gly Gly Arg Gly Gly Gly Gly Ala Gly Arg Gly Gly Gly Ala Ala Gly
        355                 360                 365
Pro Arg Glu Gly Ala Ser Ser Pro Gly Ala Arg Arg Gly Glu Gln Arg
    370                 375                 380
Arg Arg Gly Arg Gly Pro Pro Ala Ala Gly Ala Ala Gln Val Ser Ala
385                 390                 395                 400
Arg Gly Arg Arg Ala Arg Gly Gln Arg Ala Gly Glu Glu Ala Gln Asp
                405                 410                 415
Gly Leu Leu Pro Arg Gly Arg Asp Arg Leu Pro Leu Arg Pro Gly Asp
            420                 425                 430
Ala Asn Gln Arg Ala Glu Arg Pro Gly Pro Pro Arg Gly Gly His Gly
        435                 440                 445
Pro Val Asn Ala Ser Ser Ala Pro Asp Thr Ser Pro Pro Arg His Pro
    450                 455                 460
Arg Arg Trp Val Ser Gln Gln Arg Gln Arg Leu Trp Arg Gln Phe Arg
465                 470                 475                 480
Val Gly Gly Gly Phe Pro Pro Pro Pro Pro Ser Arg Pro Pro Ala Val
                485                 490                 495
Leu Leu Pro Leu Leu Arg Leu Ala Cys Ala Gly Asp Pro Gly Ala Thr
            500                 505                 510
Arg Pro Gly Pro Arg Arg Pro Ala Arg Arg Pro Arg Gly Glu Leu Ile
        515                 520                 525
Pro Arg Arg Pro Asp Pro Ala Ala Pro Ser Glu Glu Gly Leu Arg Met
    530                 535                 540
Glu Ser Ser Val Asp Asp Gly Ala Thr Ala Thr Thr Ala Asp Ala Ala
545                 550                 555                 560
Ser Gly Glu Ala Pro Glu Ala Gly Pro Ser Pro Ser His Ser Pro Thr
                565                 570                 575
Met Cys Gln Thr Gly Gly Pro Gly Pro Pro Pro Pro Gln Pro Pro Arg
            580                 585                 590
Trp Leu Pro
        595

      <210> 188
      <211> 376
      <212> PRT
      <213> Homo sapien

      <400> 188
Glu Met Arg Lys Phe Asp Val Pro Ser Met Glu Ser Thr Leu Asn Gln
 1               5                  10                  15
Pro Ala Met Leu Glu Thr Leu Tyr Ser Asp Pro His Tyr Arg Ala His
            20                  25                  30
Phe Pro Asn Pro Arg Pro Asp Thr Asn Lys Asp Val Tyr Lys Val Leu
        35                  40                  45
```

```
Pro Glu Ser Lys Lys Ala Pro Gly Ser Gly Ala Val Phe Glu Arg Asn
    50                  55                  60
Gly Pro His Ala Ser Ser Ser Gly Val Leu Pro Leu Gly Leu Gln Pro
65                  70                  75                  80
Ala Pro Gly Leu Ser Lys Ser Leu Ser Ser Gln Val Trp Gln Pro Ser
                85                  90                  95
Pro Asp Pro Trp His Pro Gly Glu Gln Ser Cys Glu Leu Ser Thr Cys
            100                 105                 110
Arg Gln Gln Leu Glu Leu Ile Arg Leu Gln Met Glu Gln Met Gln Leu
        115                 120                 125
Gln Asn Gly Ala Met Cys His His Pro Ala Ala Phe Ala Pro Leu Leu
    130                 135                 140
Pro Thr Leu Glu Pro Ala Gln Trp Leu Ser Ile Leu Asn Ser Asn Glu
145                 150                 155                 160
His Leu Leu Lys Glu Lys Glu Leu Leu Ile Asp Lys Gln Arg Lys His
                165                 170                 175
Ile Ser Gln Leu Glu Gln Lys Val Arg Glu Ser Glu Leu Gln Val His
            180                 185                 190
Ser Ala Leu Leu Gly Arg Pro Ala Pro Phe Gly Asp Val Cys Leu Leu
        195                 200                 205
Arg Leu Gln Glu Leu Gln Arg Glu Asn Thr Phe Leu Arg Ala Gln Phe
    210                 215                 220
Ala Gln Lys Thr Glu Ala Leu Ser Lys Glu Lys Met Glu Leu Glu Lys
225                 230                 235                 240
Lys Leu Ser Ala Ser Glu Val Glu Ile Gln Leu Ile Arg Glu Ser Leu
                245                 250                 255
Lys Val Thr Leu Gln Lys His Ser Glu Glu Gly Lys Lys Gln Glu Glu
            260                 265                 270
Arg Val Lys Gly Arg Asp Lys His Ile Asn Asn Leu Lys Lys Lys Cys
        275                 280                 285
Gln Lys Glu Ser Glu Gln Asn Arg Glu Lys Gln Gln Arg Ile Glu Thr
    290                 295                 300
Leu Glu Arg Tyr Leu Ala Asp Leu Pro Thr Leu Glu Asp His Gln Lys
305                 310                 315                 320
Gln Thr Glu Gln Leu Lys Asp Ala Glu Leu Lys Asn Thr Glu Leu Gln
                325                 330                 335
Glu Arg Val Ala Glu Leu Glu Thr Leu Leu Glu Asp Thr Gln Ala Thr
            340                 345                 350
Cys Arg Glu Lys Glu Val Gln Leu Glu Ser Leu Arg Gln Arg Glu Ala
        355                 360                 365
Asp Leu Ser Ser Ala Arg His Arg
    370                 375

      <210> 189
      <211> 160
      <212> PRT
      <213> Homo sapien

      <400> 189
Met Leu Glu Ala His Arg Arg Gln Arg His Pro Phe Leu Leu Leu Gly
 1               5                  10                  15
Thr Thr Ala Asn Arg Thr Gln Ser Leu Asn Tyr Gly Cys Ile Val Glu
            20                  25                  30
Asn Pro Gln Thr His Glu Val Leu His Tyr Val Glu Lys Pro Ser Thr
        35                  40                  45
Phe Ile Ser Asp Ile Ile Asn Cys Gly Ile Tyr Leu Phe Ser Pro Glu
    50                  55                  60
Ala Leu Lys Pro Leu Arg Asp Val Phe Gln Arg Asn Gln Gln Asp Gly
```

65 70 75 80
Gln Leu Glu Asp Ser Pro Gly Leu Trp Pro Gly Ala Gly Thr Ile Arg
85 90 95
Leu Glu Gln Asp Val Phe Ser Ala Leu Ala Gly Gln Gly Gln Ile Tyr
100 105 110
Val His Leu Thr Asp Gly Ile Trp Ser Gln Ile Lys Ser Ala Gly Ser
115 120 125
Ala Leu Tyr Ala Ser Arg Leu Tyr Leu Ser Arg Tyr Gln Asp Thr His
130 135 140
Pro Glu Arg Leu Ala Lys His Thr Pro Gly Gly Pro Trp Ile Arg Gly
145 150 155 160

<210> 190
<211> 146
<212> PRT
<213> Homo sapien

<400> 190
Met Asp Pro Arg Ala Ser Leu Leu Leu Leu Gly Asn Val Tyr Ile His
1 5 10 15
Pro Thr Ala Lys Val Ala Pro Ser Ala Val Leu Gly Pro Asn Val Ser
20 25 30
Ile Gly Lys Gly Val Thr Val Gly Glu Gly Val Arg Leu Arg Glu Ser
35 40 45
Ile Val Leu His Gly Ala Thr Leu Gln Glu His Thr Cys Val Leu His
50 55 60
Ser Ile Val Gly Trp Gly Ser Thr Val Gly Arg Trp Ala Arg Val Glu
65 70 75 80
Gly Thr Pro Ser Asp Pro Asn Pro Asn Asp Pro Arg Ala Arg Met Asp
85 90 95
Ser Glu Ser Leu Phe Lys Asp Gly Lys Leu Leu Pro Ala Ile Thr Ile
100 105 110
Leu Gly Cys Arg Val Arg Ile Pro Ala Glu Val Leu Ile Leu Asn Ser
115 120 125
Ile Val Leu Pro His Lys Glu Leu Ser Arg Ser Phe Thr Asn Gln Ile
130 135 140
Ile Leu
145

<210> 191
<211> 704
<212> PRT
<213> Homo sapien

<400> 191
Glu Gly Gly Cys Ala Ala Gly Arg Gly Arg Glu Leu Glu Pro Glu Leu
1 5 10 15
Glu Pro Gly Pro Gly Pro Gly Ser Ala Leu Glu Pro Gly Glu Glu Phe
20 25 30
Glu Ile Val Asp Arg Ser Gln Leu Pro Gly Pro Gly Asp Leu Arg Ser
35 40 45
Ala Thr Arg Pro Arg Ala Ala Glu Gly Trp Ser Ala Pro Ile Leu Thr
50 55 60
Leu Ala Arg Arg Ala Thr Gly Asn Leu Ser Ala Ser Cys Gly Ser Ala
65 70 75 80
Leu Arg Ala Ala Ala Gly Leu Gly Gly Gly Asp Ser Gly Asp Gly Thr
85 90 95
Ala Arg Ala Ala Ser Lys Cys Gln Met Met Glu Glu Arg Ala Asn Leu

```
                100                 105                 110
Met His Met Met Lys Leu Ser Ile Lys Val Leu Leu Gln Ser Ala Leu
        115                 120                 125
Ser Leu Gly Arg Ser Leu Asp Ala Asp His Ala Pro Leu Gln Gln Phe
    130                 135                 140
Phe Val Val Met Glu His Cys Leu Lys His Gly Leu Lys Val Lys Lys
145                 150                 155                 160
Ser Phe Ile Gly Gln Asn Lys Ser Phe Phe Gly Pro Leu Glu Leu Val
                165                 170                 175
Glu Lys Leu Cys Pro Glu Ala Ser Asp Ile Ala Thr Ser Val Arg Asn
            180                 185                 190
Leu Pro Glu Leu Lys Thr Ala Val Gly Arg Gly Arg Ala Trp Leu Tyr
        195                 200                 205
Leu Ala Leu Met Gln Lys Lys Leu Ala Asp Tyr Leu Lys Val Leu Ile
    210                 215                 220
Asp Asn Lys His Leu Leu Ser Glu Phe Tyr Glu Pro Glu Ala Leu Met
225                 230                 235                 240
Met Glu Glu Glu Gly Met Val Ile Val Gly Leu Leu Val Gly Leu Asn
                245                 250                 255
Val Leu Asp Ala Asn Leu Cys Leu Lys Gly Glu Asp Leu Asp Ser Gln
            260                 265                 270
Val Gly Val Ile Asp Phe Ser Leu Tyr Leu Lys Asp Val Gln Asp Leu
        275                 280                 285
Asp Gly Gly Lys Glu His Glu Arg Ile Thr Asp Val Leu Asp Gln Lys
    290                 295                 300
Asn Tyr Val Glu Glu Leu Asn Arg His Leu Ser Cys Thr Val Gly Asp
305                 310                 315                 320
Leu Gln Thr Lys Ile Asp Gly Leu Glu Lys Thr Asn Ser Lys Leu Gln
                325                 330                 335
Glu Glu Leu Ser Ala Ala Thr Asp Arg Ile Cys Ser Leu Gln Glu Glu
            340                 345                 350
Gln Gln Gln Leu Arg Glu Gln Asn Glu Leu Ile Arg Glu Arg Ser Glu
        355                 360                 365
Lys Ser Val Glu Ile Thr Lys Gln Asp Thr Lys Val Glu Leu Glu Thr
    370                 375                 380
Tyr Lys Gln Thr Arg Gln Gly Leu Asp Glu Met Tyr Ser Asp Val Trp
385                 390                 395                 400
Lys Gln Leu Lys Glu Glu Lys Lys Val Arg Leu Glu Leu Glu Lys Glu
                405                 410                 415
Leu Glu Leu Gln Ile Gly Met Lys Thr Glu Met Glu Ile Ala Met Lys
            420                 425                 430
Leu Leu Glu Lys Asp Thr His Glu Lys Gln Asp Thr Leu Val Ala Leu
        435                 440                 445
Arg Gln Gln Leu Glu Glu Val Lys Ala Ile Asn Leu Gln Met Phe His
    450                 455                 460
Lys Ala Gln Asn Ala Glu Ser Ser Leu Gln Gln Lys Asn Glu Ala Ile
465                 470                 475                 480
Thr Ser Phe Glu Gly Lys Thr Asn Gln Val Met Ser Ser Met Lys Gln
                485                 490                 495
Met Glu Glu Arg Leu Gln His Ser Glu Arg Ala Arg Gln Gly Ala Glu
            500                 505                 510
Glu Arg Ser His Lys Leu Gln Gln Glu Leu Gly Gly Arg Ile Gly Ala
        515                 520                 525
Leu Gln Leu Gln Leu Ser Gln Leu His Glu Gln Cys Ser Ser Leu Glu
    530                 535                 540
Lys Glu Leu Lys Ser Glu Lys Glu Gln Arg Gln Ala Leu Gln Arg Glu
545                 550                 555                 560
Leu Gln His Glu Lys Asp Thr Ser Ser Leu Leu Arg Met Glu Leu Gln
```

```
                565                 570                 575
Gln Val Glu Gly Leu Lys Lys Glu Leu Arg Glu Leu Gln Asp Glu Lys
            580                 585                 590
Ala Glu Leu Gln Lys Ile Cys Glu Glu Gln Glu Gln Ala Leu Gln Glu
        595                 600                 605
Met Gly Leu His Leu Ser Gln Ser Lys Leu Lys Met Glu Asp Ile Lys
    610                 615                 620
Glu Val Asn Gln Ala Leu Lys Gly His Ala Trp Leu Lys Asp Asp Glu
625                 630                 635                 640
Ala Thr His Cys Arg Gln Cys Glu Lys Glu Phe Ser Ile Ser Arg Arg
                645                 650                 655
Lys His His Cys Arg Asn Cys Gly His Ile Phe Cys Asn Thr Cys Ser
            660                 665                 670
Ser Asn Glu Leu Ala Leu Pro Ser Tyr Pro Lys Pro Val Arg Val Cys
        675                 680                 685
Asp Ser Cys His Thr Leu Leu Leu Gln Arg Cys Ser Ser Thr Ala Ser
    690                 695                 700

      <210> 192
      <211> 331
      <212> PRT
      <213> Homo sapien

      <400> 192
Arg Ala Gly Ala Ser Ala Met Ala Leu Arg Lys Glu Leu Leu Lys Ser
 1               5                  10                  15
Ile Trp Tyr Ala Phe Thr Ala Leu Asp Val Glu Lys Ser Gly Lys Val
            20                  25                  30
Ser Lys Ser Gln Leu Lys Val Leu Ser His Asn Leu Tyr Thr Val Leu
        35                  40                  45
His Ile Pro His Asp Pro Val Ala Leu Glu Glu His Phe Arg Asp Asp
    50                  55                  60
Asp Asp Gly Pro Val Ser Ser Gln Gly Tyr Met Pro Tyr Leu Asn Lys
65                  70                  75                  80
Tyr Ile Leu Asp Lys Val Glu Glu Gly Ala Phe Val Lys Glu His Phe
                85                  90                  95
Asp Glu Leu Cys Trp Thr Leu Thr Ala Lys Lys Asn Tyr Arg Ala Asp
            100                 105                 110
Ser Asn Gly Asn Ser Met Leu Ser Asn Gln Asp Ala Phe Arg Leu Trp
        115                 120                 125
Cys Leu Phe Asn Phe Leu Ser Glu Asp Lys Tyr Pro Leu Ile Met Val
    130                 135                 140
Pro Asp Glu Val Glu Tyr Leu Leu Lys Lys Val Leu Ser Ser Met Ser
145                 150                 155                 160
Leu Glu Val Ser Leu Gly Glu Leu Glu Glu Leu Leu Ala Gln Glu Ala
                165                 170                 175
Gln Val Ala Gln Thr Thr Gly Gly Leu Ser Val Trp Gln Phe Leu Glu
            180                 185                 190
Leu Phe Asn Ser Gly Arg Cys Leu Arg Gly Val Gly Arg Asp Thr Leu
        195                 200                 205
Ser Met Ala Ile His Glu Val Tyr Gln Glu Leu Ile Gln Asp Val Leu
    210                 215                 220
Lys Gln Gly Tyr Leu Trp Lys Arg Gly His Leu Arg Arg Asn Trp Ala
225                 230                 235                 240
Glu Arg Trp Phe Gln Leu Gln Pro Ser Cys Leu Cys Tyr Phe Gly Ser
                245                 250                 255
Glu Glu Cys Lys Glu Lys Arg Gly Ile Ile Pro Leu Asp Ala His Cys
            260                 265                 270
```

```
Cys Val Glu Val Leu Pro Asp Arg Asp Gly Lys Arg Cys Met Phe Cys
        275                 280                 285
Val Lys Thr Ala Thr Arg Thr Tyr Glu Met Ser Ala Ser Asp Thr Arg
    290                 295                 300
Gln Arg Gln Glu Trp Thr Ala Ala Ile Gln Met Ala Ile Arg Leu Gln
305                 310                 315                 320
Ala Glu Gly Lys Thr Ser Leu His Lys Asp Leu
                325                 330
```

<210> 193
<211> 475
<212> PRT
<213> Homo sapien

<400> 193

```
Lys Asn Ser Pro Leu Leu Ser Val Ser Ser Gln Thr Ile Thr Lys Glu
 1               5                  10                  15
Asn Asn Arg Asn Val His Leu Glu His Ser Glu Gln Asn Pro Gly Ser
            20                  25                  30
Ser Ala Gly Asp Thr Ser Ala Ala His Gln Val Val Leu Gly Glu Asn
        35                  40                  45
Leu Ile Ala Thr Ala Leu Cys Leu Ser Gly Ser Gly Ser Gln Ser Asp
    50                  55                  60
Leu Lys Asp Val Ala Ser Thr Ala Gly Glu Glu Gly Asp Thr Ser Leu
65                  70                  75                  80
Arg Glu Ser Leu His Pro Val Thr Arg Ser Leu Lys Ala Gly Cys His
                85                  90                  95
Thr Lys Gln Leu Ala Ser Arg Asn Cys Ser Glu Glu Lys Ser Pro Gln
            100                 105                 110
Thr Ser Ile Leu Lys Glu Gly Asn Arg Asp Thr Ser Leu Asp Phe Arg
        115                 120                 125
Pro Val Val Ser Pro Ala Asn Gly Val Glu Gly Val Arg Val Asp Gln
    130                 135                 140
Asp Asp Asp Gln Asp Ser Ser Ser Leu Lys Leu Ser Gln Asn Ile Ala
145                 150                 155                 160
Val Gln Thr Asp Phe Lys Thr Ala Asp Ser Glu Val Asn Thr Asp Gln
                165                 170                 175
Asp Ile Glu Lys Asn Leu Asp Lys Met Met Thr Glu Arg Thr Leu Leu
            180                 185                 190
Lys Glu Arg Tyr Gln Glu Val Leu Asp Lys Gln Arg Gln Val Glu Asn
        195                 200                 205
Gln Leu Gln Val Gln Leu Lys Gln Leu Gln Gln Arg Arg Glu Glu Glu
    210                 215                 220
Met Lys Asn His Gln Glu Ile Leu Lys Ala Ile Gln Asp Val Thr Ile
225                 230                 235                 240
Lys Arg Glu Glu Thr Lys Lys Lys Ile Glu Lys Glu Lys Lys Glu Phe
                245                 250                 255
Leu Gln Lys Glu Gln Asp Leu Lys Ala Glu Ile Glu Lys Leu Cys Glu
            260                 265                 270
Lys Gly Arg Arg Glu Val Trp Glu Met Glu Leu Asp Arg Leu Lys Asn
        275                 280                 285
Gln Asp Gly Glu Ile Asn Arg Asn Ile Met Glu Glu Thr Glu Arg Ala
    290                 295                 300
Trp Lys Ala Glu Ile Leu Ser Leu Glu Ser Arg Lys Glu Leu Leu Val
305                 310                 315                 320
Leu Lys Leu Glu Glu Ala Glu Lys Glu Ala Glu Leu His Leu Thr Tyr
                325                 330                 335
Leu Lys Ser Thr Pro Pro Thr Leu Glu Thr Val Arg Ser Lys Gln Glu
```

```
            340                 345                 350
Trp Glu Thr Arg Leu Asn Gly Val Arg Ile Met Lys Lys Asn Val Arg
        355                 360                 365
Asp Gln Phe Asn Ser His Ile Gln Leu Val Arg Asn Gly Ala Lys Leu
    370                 375                 380
Ser Ser Leu Pro Gln Ile Pro Thr Pro Thr Leu Pro Pro Pro Pro Ser
385                 390                 395                 400
Glu Thr Asp Phe Met Leu Gln Val Phe Gln Pro Ser Pro Ser Leu Ala
                405                 410                 415
Pro Arg Met Pro Phe Ser Ile Gly Gln Val Thr Met Pro Met Val Met
            420                 425                 430
Pro Ser Ala Asp Pro Arg Ser Leu Ser Phe Pro Ile Leu Asn Pro Ala
        435                 440                 445
Leu Ser Gln Pro Ser Gln Pro Ser Ser Pro Leu Pro Gly Ser His Gly
    450                 455                 460
Arg Asn Ser Pro Gly Leu Gly Ser Leu Val Ser
465                 470                 475

      <210> 194
      <211> 241
      <212> PRT
      <213> Homo sapien

      <400> 194
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
 1                5                  10                  15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
            20                  25                  30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
        35                  40                  45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
    50                  55                  60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
65                  70                  75                  80
Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
                85                  90                  95
Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
            100                 105                 110
Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
        115                 120                 125
Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Ala Gly Leu Lys Glu
    130                 135                 140
Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
145                 150                 155                 160
Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
                165                 170                 175
Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
            180                 185                 190
Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu
        195                 200                 205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
    210                 215                 220
Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
225                 230                 235                 240
Leu

      <210> 195
```

<211> 138
<212> PRT
<213> Homo sapien

<400> 195
Gln Thr Lys Ile Leu Glu Glu Asp Leu Glu Gln Ile Lys Leu Ser Leu
1 5 10 15
Arg Glu Arg Gly Arg Glu Leu Thr Thr Gln Arg Gln Leu Met Gln Glu
20 25 30
Arg Ala Glu Glu Gly Lys Gly Pro Ser Lys Ala Gln Arg Gly Ser Leu
35 40 45
Glu His Met Lys Leu Ile Leu Arg Asp Lys Glu Lys Glu Val Glu Cys
50 55 60
Gln Gln Glu His Ile His Glu Leu Gln Glu Leu Lys Asp Gln Leu Glu
65 70 75 80
Gln Gln Leu Gln Gly Leu His Arg Lys Val Gly Glu Thr Ser Leu Leu
85 90 95
Leu Ser Gln Arg Glu Gln Glu Ile Val Val Leu Gln Gln Gln Leu Gln
100 105 110
Glu Ala Arg Glu Gln Gly Glu Leu Lys Glu Gln Ser Leu Gln Ser Gln
115 120 125
Leu Asp Glu Ala Gln Arg Ala Leu Ala Gln
130 135

<210> 196
<211> 102
<212> PRT
<213> Homo sapien

<400> 196
Met Ser Lys Arg Lys Ala Pro Gln Glu Thr Leu Asn Gly Gly Ile Thr
1 5 10 15
Asp Met Leu Thr Glu Leu Ala Asn Phe Glu Lys Asn Val Ser Gln Ala
20 25 30
Ile His Lys Tyr Asn Ala Tyr Arg Lys Ala Ala Ser Val Ile Ala Lys
35 40 45
Tyr Pro His Lys Ile Lys Ser Gly Ala Glu Ala Lys Lys Leu Pro Gly
50 55 60
Val Gly Thr Lys Ile Ala Glu Lys Ile Asp Glu Phe Leu Ala Thr Gly
65 70 75 80
Lys Leu Arg Lys Leu Glu Lys Ile Arg Gln Asp Asp Thr Ser Ser Ser
85 90 95
Ile Asn Phe Leu Thr Arg
100

<210> 197
<211> 138
<212> PRT
<213> Homo sapien

<400> 197
Glu Ala Asn Glu Val Thr Asp Ser Ala Tyr Met Gly Ser Glu Ser Thr
1 5 10 15
Tyr Ser Glu Cys Glu Thr Phe Thr Asp Glu Asp Thr Ser Thr Leu Val
20 25 30
His Pro Glu Leu Gln Pro Glu Gly Asp Ala Asp Ser Ala Gly Gly Ser
35 40 45
Ala Val Pro Ser Glu Cys Leu Asp Ala Met Glu Glu Pro Asp His Gly

```
    50                  55                  60
Ala Leu Leu Leu Leu Pro Gly Arg Pro His Pro His Gly Gln Ser Val
65                  70                  75                  80
Ile Thr Val Ile Gly Gly Glu Glu His Phe Glu Asp Tyr Gly Glu Gly
                85                  90                  95
Ser Glu Ala Glu Leu Ser Pro Glu Thr Leu Cys Asn Gly Gln Leu Gly
            100                 105                 110
Cys Ser Asp Pro Ala Phe Leu Thr Pro Ser Pro Thr Lys Arg Leu Ser
        115                 120                 125
Ser Lys Lys Val Ala Arg Tyr Leu His Gln
    130                 135
```

<210> 198
<211> 100
<212> PRT
<213> Homo sapien

<400> 198

```
Met Gly Asp Val Lys Asn Phe Leu Tyr Ala Trp Cys Gly Lys Arg Lys
 1               5                  10                  15
Met Thr Pro Ser Tyr Glu Ile Arg Ala Val Gly Asn Lys Asn Arg Gln
            20                  25                  30
Lys Phe Met Cys Glu Val Gln Val Glu Gly Tyr Asn Tyr Thr Gly Met
        35                  40                  45
Gly Asn Ser Thr Asn Lys Lys Asp Ala Gln Ser Asn Ala Ala Arg Asp
    50                  55                  60
Phe Val Asn Tyr Leu Val Arg Ile Asn Glu Ile Lys Ser Glu Glu Val
65                  70                  75                  80
Pro Ala Phe Gly Val Ala Ser Pro Pro Pro Leu Thr Asp Thr Pro Asp
                85                  90                  95
Thr Thr Ala Asn
            100
```

<210> 199
<211> 127
<212> PRT
<213> Homo sapien

<400> 199

```
Met Val Lys Glu Thr Thr Tyr Tyr Asp Val Leu Gly Val Lys Pro Asn
 1               5                  10                  15
Ala Thr Gln Glu Glu Leu Lys Lys Ala Tyr Arg Lys Leu Ala Leu Lys
            20                  25                  30
Tyr His Pro Asp Lys Asn Pro Asn Glu Gly Glu Lys Phe Lys Gln Ile
        35                  40                  45
Ser Gln Ala Tyr Glu Val Leu Ser Asp Ala Lys Lys Arg Glu Leu Tyr
    50                  55                  60
Asp Lys Gly Gly Glu Gln Ala Ile Lys Glu Gly Gly Ala Gly Gly Gly
65                  70                  75                  80
Phe Gly Ser Pro Met Asp Ile Phe Asp Met Phe Phe Gly Gly Gly Gly
                85                  90                  95
Arg Met Gln Arg Glu Arg Arg Gly Lys Asn Val Val His Gln Leu Ser
            100                 105                 110
Val Thr Leu Glu Asp Leu Tyr Asn Gly Ala Thr Arg Lys Leu Ala
        115                 120                 125
```

<210> 200
<211> 90

<212> PRT
<213> Homo sapien

<400> 200
Met Ala Cys Pro Leu Asp Gln Ala Ile Gly Leu Leu Val Ala Ile Phe
1 5 10 15
His Lys Tyr Ser Gly Arg Glu Gly Asp Lys His Thr Leu Ser Lys Lys
20 25 30
Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
35 40 45
Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
50 55 60
Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
65 70 75 80
Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
85 90

<210> 201
<211> 120
<212> PRT
<213> Homo sapien

<400> 201
Met Glu Thr Pro Ser Gln Arg Arg Ala Thr Arg Ser Gly Ala Gln Ala
1 5 10 15
Ser Ser Thr Pro Leu Ser Pro Thr Arg Ile Thr Arg Leu Gln Glu Lys
20 25 30
Glu Asp Leu Gln Glu Leu Asn Asp Arg Leu Ala Val Tyr Ile Asp Arg
35 40 45
Val Arg Ser Leu Glu Thr Glu Asn Ala Gly Leu Arg Leu Arg Ile Thr
50 55 60
Glu Ser Glu Glu Val Val Ser Arg Glu Val Ser Gly Ile Lys Ala Ala
65 70 75 80
Tyr Glu Ala Glu Leu Gly Asp Ala Arg Lys Thr Leu Asp Ser Val Ala
85 90 95
Lys Glu Arg Ala Arg Leu Gln Leu Glu Leu Ser Lys Val Arg Glu Glu
100 105 110
Phe Lys Glu Leu Lys Ala Arg Asn
115 120

<210> 202
<211> 177
<212> PRT
<213> Homo sapien

<400> 202
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
1 5 10 15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
20 25 30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
35 40 45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
50 55 60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65 70 75 80
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
85 90 95

```
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
            100                 105                 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
        115                 120                 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
    130                 135                 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Ala
145                 150                 155                 160
Gly Arg Leu Gly Ser Thr Val Phe Val Ala Asn Leu Asp Tyr Lys Val
                165                 170                 175
Gly
```

<210> 203
<211> 164
<212> PRT
<213> Homo sapien

<400> 203

```
Met Arg Leu Ala Val Gly Ala Leu Leu Val Cys Ala Val Leu Gly Leu
 1               5                  10                  15
Cys Leu Ala Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu
            20                  25                  30
His Glu Ala Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val
        35                  40                  45
Ile Pro Ser Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr
    50                  55                  60
Leu Asp Cys Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr
65                  70                  75                  80
Leu Asp Ala Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu
                85                  90                  95
Lys Pro Val Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr
            100                 105                 110
Phe Tyr Tyr Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met
        115                 120                 125
Asn Gln Leu Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser
    130                 135                 140
Ala Gly Trp Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu
145                 150                 155                 160
Pro Arg Lys Pro
```

<210> 204
<211> 241
<212> PRT
<213> Homo sapien

<400> 204

```
Met Ser Gly Glu Ser Ala Arg Ser Leu Gly Lys Gly Ser Ala Pro Pro
 1               5                  10                  15
Gly Pro Val Pro Glu Gly Ser Ile Arg Ile Tyr Ser Met Arg Phe Cys
            20                  25                  30
Pro Phe Ala Glu Arg Thr Arg Leu Val Leu Lys Ala Lys Gly Ile Arg
        35                  40                  45
His Glu Val Ile Asn Ile Asn Leu Lys Asn Lys Pro Glu Trp Phe Phe
    50                  55                  60
Lys Lys Asn Pro Phe Gly Leu Val Pro Val Leu Glu Asn Ser Gln Gly
65                  70                  75                  80
```

```
Gln Leu Ile Tyr Glu Ser Ala Ile Thr Cys Glu Tyr Leu Asp Glu Ala
                85                  90                  95
Tyr Pro Gly Lys Lys Leu Leu Pro Asp Asp Pro Tyr Glu Lys Ala Cys
            100                 105                 110
Gln Lys Met Ile Leu Glu Leu Phe Ser Lys Val Pro Ser Leu Val Gly
        115                 120                 125
Ser Phe Ile Arg Ser Gln Asn Lys Glu Asp Tyr Asp Gly Leu Lys Glu
    130                 135                 140
Glu Phe Arg Lys Glu Phe Thr Lys Leu Glu Glu Val Leu Thr Asn Lys
145                 150                 155                 160
Lys Thr Thr Phe Phe Gly Gly Asn Ser Ile Ser Met Ile Asp Tyr Leu
                165                 170                 175
Ile Trp Pro Trp Phe Glu Arg Leu Glu Ala Met Lys Leu Asn Glu Cys
            180                 185                 190
Val Asp His Thr Pro Lys Leu Lys Leu Trp Met Ala Ala Met Lys Glu
        195                 200                 205
Asp Pro Thr Val Ser Ala Leu Leu Thr Ser Glu Lys Asp Trp Gln Gly
    210                 215                 220
Phe Leu Glu Leu Tyr Leu Gln Asn Ser Pro Glu Ala Cys Asp Tyr Gly
225                 230                 235                 240
Leu
```

<210> 205
<211> 160
<212> PRT
<213> Homo sapien

<400> 205

```
Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu
 1               5                  10                  15
Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp
            20                  25                  30
Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys
        35                  40                  45
Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu
    50                  55                  60
Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe
65                  70                  75                  80
Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser
                85                  90                  95
Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile
            100                 105                 110
Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp
        115                 120                 125
Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His
    130                 135                 140
Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu
145                 150                 155                 160
```

<210> 206
<211> 197
<212> PRT
<213> Homo sapien

<400> 206

```
Thr Ser Pro Ser Glu Ala Cys Ala Pro Leu Leu Ile Ser Leu Ser Thr
 1               5                  10                  15
```

```
Leu Ile Tyr Asn Gly Ala Leu Pro Cys Gln Cys Asn Pro Gln Gly Ser
            20                  25                  30
Leu Ser Ser Glu Cys Asn Pro His Gly Gly Gln Cys Leu Cys Lys Pro
        35                  40                  45
Gly Val Val Gly Arg Arg Cys Asp Leu Cys Ala Pro Gly Tyr Tyr Gly
    50                  55                  60
Phe Gly Pro Thr Gly Cys Gln Gly Ala Cys Leu Gly Cys Arg Asp His
65                  70                  75                  80
Thr Gly Gly Glu His Cys Glu Arg Cys Ile Ala Gly Phe His Gly Asp
                85                  90                  95
Pro Arg Leu Pro Tyr Gly Gly Gln Cys Arg Pro Cys Pro Cys Pro Glu
            100                 105                 110
Gly Pro Gly Ser Gln Arg His Phe Ala Thr Ser Cys His Gln Asp Glu
        115                 120                 125
Tyr Ser Gln Gln Ile Val Cys His Cys Arg Ala Gly Tyr Thr Gly Leu
    130                 135                 140
Arg Cys Glu Ala Cys Ala Pro Gly His Phe Gly Asp Pro Ser Arg Pro
145                 150                 155                 160
Gly Gly Arg Cys Gln Leu Cys Glu Cys Ser Gly Asn Ile Asp Pro Met
                165                 170                 175
Asp Pro Asp Ala Cys Asp Pro His Thr Gly Gln Cys Leu Arg Cys Leu
            180                 185                 190
His His Thr Glu Gly
        195
```

<210> 207
<211> 175
<212> PRT
<213> Homo sapien

<400> 207

```
Ile Ile Arg Gln Gln Gly Leu Ala Ser Tyr Asp Tyr Val Arg Arg Arg
 1               5                  10                  15
Leu Thr Ala Glu Asp Leu Phe Glu Ala Arg Ile Ile Ser Leu Glu Thr
            20                  25                  30
Tyr Asn Leu Leu Arg Glu Gly Thr Arg Ser Leu Arg Glu Ala Leu Glu
        35                  40                  45
Ala Glu Ser Ala Trp Cys Tyr Leu Tyr Gly Thr Gly Ser Val Ala Gly
    50                  55                  60
Val Tyr Leu Pro Gly Ser Arg Gln Thr Leu Ser Ile Tyr Gln Ala Leu
65                  70                  75                  80
Lys Lys Gly Leu Leu Ser Ala Glu Val Ala Arg Leu Leu Leu Glu Ala
                85                  90                  95
Gln Ala Ala Thr Gly Phe Leu Leu Asp Pro Val Lys Gly Glu Arg Leu
            100                 105                 110
Thr Val Asp Glu Ala Val Arg Lys Gly Leu Val Gly Pro Glu Leu His
        115                 120                 125
Asp Arg Leu Leu Ser Ala Glu Arg Ala Val Thr Gly Tyr Arg Asp Pro
    130                 135                 140
Tyr Thr Glu Gln Thr Ile Ser Leu Phe Gln Ala Met Lys Lys Glu Leu
145                 150                 155                 160
Ile Pro Thr Glu Glu Ala Leu Arg Leu Trp Met Pro Ser Trp Pro
                165                 170                 175
```

<210> 208
<211> 177
<212> PRT
<213> Homo sapien

<400> 208

```
Met Ala Ala Gly Val Glu Ala Ala Ala Glu Val Ala Ala Thr Glu Ile
 1               5                  10                  15
Lys Met Glu Glu Glu Ser Gly Ala Pro Gly Val Pro Ser Gly Asn Gly
            20                  25                  30
Ala Pro Gly Pro Lys Gly Glu Gly Glu Arg Pro Ala Gln Asn Glu Lys
        35                  40                  45
Arg Lys Glu Lys Asn Ile Lys Arg Gly Gly Asn Arg Phe Glu Pro Tyr
    50                  55                  60
Ala Asn Pro Thr Lys Arg Tyr Arg Ala Phe Ile Thr Asn Ile Pro Phe
65                  70                  75                  80
Asp Val Lys Trp Gln Ser Leu Lys Asp Leu Val Lys Glu Lys Val Gly
                85                  90                  95
Glu Val Thr Tyr Val Glu Leu Leu Met Asp Ala Glu Gly Lys Ser Arg
            100                 105                 110
Gly Cys Ala Val Val Glu Phe Lys Met Glu Glu Ser Met Lys Lys Ala
        115                 120                 125
Ala Glu Val Leu Asn Lys His Ser Leu Ser Gly Arg Pro Leu Lys Val
    130                 135                 140
Lys Glu Asp Pro Asp Gly Glu His Ala Arg Arg Ala Met Gln Lys Val
145                 150                 155                 160
Met Ala Thr Thr Gly Gly Met Gly Met Gly Pro Gly Gly Pro Gly Met
                165                 170                 175
Ile
```

<210> 209
<211> 196
<212> PRT
<213> Homo sapien

<400> 209

```
Asp Leu Gln Asp Met Phe Ile Val His Thr Ile Glu Glu Ile Glu Gly
 1               5                  10                  15
Leu Ile Ser Ala His Asp Gln Phe Lys Ser Thr Leu Pro Asp Ala Asp
            20                  25                  30
Arg Glu Arg Glu Ala Ile Leu Ala Ile His Lys Glu Ala Gln Arg Ile
        35                  40                  45
Ala Glu Ser Asn His Ile Lys Leu Ser Gly Ser Asn Pro Tyr Thr Thr
    50                  55                  60
Val Thr Pro Gln Ile Ile Asn Ser Lys Trp Glu Lys Val Gln Gln Leu
65                  70                  75                  80
Val Pro Lys Arg Asp His Ala Leu Leu Glu Glu Gln Ser Lys Gln Gln
                85                  90                  95
Ser Asn Glu His Leu Arg Arg Gln Phe Ala Ser Gln Ala Asn Val Val
            100                 105                 110
Gly Pro Trp Ile Gln Thr Lys Met Glu Glu Ile Gly Arg Ile Ser Ile
        115                 120                 125
Glu Met Asn Gly Thr Leu Glu Asp Gln Leu Ser His Leu Lys Gln Tyr
    130                 135                 140
Glu Arg Ser Ile Val Asp Tyr Lys Pro Asn Leu Asp Leu Leu Glu Gln
145                 150                 155                 160
Gln His Gln Leu Ile Gln Glu Ala Leu Ile Phe Asp Asn Lys His Thr
                165                 170                 175
Asn Tyr Thr Met Glu His Ile Arg Val Gly Trp Glu Gln Leu Leu Thr
            180                 185                 190
Thr Ile Ala Arg
```

195

<210> 210
<211> 156
<212> PRT
<213> Homo sapien

<400> 210

```
Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly Lys Glu
 1               5                  10                  15
Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly Tyr Ser
            20                  25                  30
Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val Gly Tyr
        35                  40                  45
Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser Gly Arg
    50                  55                  60
Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val Thr Gln
65                  70                  75                  80
Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp Leu Val
                85                  90                  95
Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu Pro Lys
            100                 105                 110
Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys Asp Ala
        115                 120                 125
Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr Leu Trp
    130                 135                 140
Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Lys
145                 150                 155
```

<210> 211
<211> 92
<212> PRT
<213> Homo sapien

<400> 211

```
Met Glu Ser Pro Ser Ala Pro Pro His Arg Trp Cys Ile Pro Trp Gln
 1               5                  10                  15
Arg Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr
            20                  25                  30
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly
        35                  40                  45
Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly
    50                  55                  60
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Ile
65                  70                  75                  80
Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly
                85                  90
```

<210> 212
<211> 142
<212> PRT
<213> Homo sapien

<400> 212

```
Glu Lys Gln Lys Asn Lys Glu Phe Ser Gln Thr Leu Glu Asn Glu Lys
 1               5                  10                  15
Asn Thr Leu Leu Ser Gln Ile Ser Thr Lys Asp Gly Glu Leu Lys Met
            20                  25                  30
```

```
Leu Gln Glu Glu Val Thr Lys Met Asn Leu Leu Asn Gln Gln Ile Gln
        35                  40                  45
Glu Glu Leu Ser Arg Val Thr Lys Leu Lys Glu Thr Ala Glu Glu Glu
    50                  55                  60
Lys Asp Asp Leu Glu Glu Arg Leu Met Asn Gln Leu Ala Glu Leu Asn
65                  70                  75                  80
Gly Ser Ile Gly Asn Tyr Cys Gln Asp Val Thr Asp Ala Gln Ile Lys
                85                  90                  95
Asn Glu Leu Leu Glu Ser Glu Met Lys Asn Leu Lys Lys Cys Val Ser
            100                 105                 110
Glu Leu Glu Glu Glu Lys Gln Gln Leu Val Lys Glu Lys Thr Lys Val
        115                 120                 125
Glu Ser Glu Ile Arg Lys Glu Tyr Leu Glu Lys Ile Gln Gly
    130                 135                 140
```

<210> 213
<211> 142
<212> PRT
<213> Homo sapien

<400> 213

```
Gly Gly Tyr Gly Gly Gly Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly
 1               5                  10                  15
Leu Leu Ala Gly Asn Glu Lys Leu Thr Met Gln Asn Leu Asn Asp Arg
            20                  25                  30
Leu Ala Ser Tyr Leu Asp Lys Val Arg Ala Leu Glu Ala Ala Asn Gly
        35                  40                  45
Glu Leu Glu Val Lys Ile Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly
    50                  55                  60
Pro Ser Arg Asp Tyr Ser His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg
65                  70                  75                  80
Asp Lys Ile Leu Gly Ala Thr Ile Glu Asn Ser Arg Ile Val Leu Gln
                85                  90                  95
Ile Asp Asn Ala Arg Leu Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu
            100                 105                 110
Thr Glu Gln Ala Leu Arg Met Ser Val Glu Ala Asp Ile Asn Gly Leu
        115                 120                 125
Arg Arg Val Leu Asp Glu Leu Thr Leu Ala Arg Thr Asp Leu
    130                 135                 140
```

<210> 214
<211> 129
<212> PRT
<213> Homo sapien

<400> 214

```
Val Met Arg Val Asp Phe Asn Val Pro Met Lys Asn Asn Gln Ile Thr
 1               5                  10                  15
Asn Asn Gln Arg Ile Lys Ala Ala Val Pro Ser Ile Lys Phe Cys Leu
            20                  25                  30
Asp Asn Gly Ala Lys Ser Val Val Leu Met Ser His Leu Gly Arg Pro
        35                  40                  45
Asp Gly Val Pro Met Pro Asp Lys Tyr Ser Leu Glu Pro Val Ala Val
    50                  55                  60
Glu Leu Arg Ser Leu Leu Gly Lys Asp Val Leu Phe Leu Lys Asp Cys
65                  70                  75                  80
Val Gly Pro Glu Val Glu Lys Ala Cys Ala Asn Pro Ala Ala Gly Ser
                85                  90                  95
```

```
Val Ile Leu Leu Glu Asn Leu Arg Phe His Val Glu Glu Glu Gly Lys
            100                 105                 110
Gly Lys Asp Ala Ser Gly Asn Lys Val Lys Ala Glu Pro Ala Lys Ile
        115                 120                 125
Glu
```

<210> 215
<211> 148
<212> PRT
<213> Homo sapien

<400> 215

```
Met Ala Thr Leu Lys Glu Lys Leu Ile Ala Pro Val Ala Glu Glu Glu
 1               5                  10                  15
Ala Thr Val Pro Asn Asn Lys Ile Thr Val Val Gly Val Gly Gln Val
            20                  25                  30
Gly Met Ala Cys Ala Ile Ser Ile Leu Gly Lys Ser Leu Ala Asp Glu
        35                  40                  45
Leu Ala Leu Val Asp Val Leu Glu Asp Lys Leu Lys Gly Glu Met Met
    50                  55                  60
Asp Leu Gln His Gly Ser Leu Phe Leu Gln Thr Pro Lys Ile Val Ala
65                  70                  75                  80
Asp Lys Asp Tyr Ser Val Thr Ala Asn Ser Lys Ile Val Val Val Thr
                85                  90                  95
Ala Gly Val Arg Gln Gln Glu Gly Glu Ser Arg Leu Asn Leu Val Gln
            100                 105                 110
Arg Asn Val Asn Val Phe Lys Phe Ile Ile Pro Gln Ile Val Lys Tyr
        115                 120                 125
Ser Pro Asp Cys Ile Ile Ile Val Val Ser Asn Pro Val Asp Ile Leu
    130                 135                 140
Thr Tyr Val Thr
145
```

<210> 216
<211> 527
<212> PRT
<213> Homo sapien

<400> 216

```
Gln Arg Ala Pro Gly Ile Glu Glu Lys Ala Ala Glu Asn Gly Ala Leu
 1               5                  10                  15
Gly Ser Pro Glu Arg Glu Glu Lys Val Leu Glu Asn Gly Glu Leu Thr
            20                  25                  30
Pro Pro Arg Arg Glu Glu Lys Ala Leu Glu Asn Gly Glu Leu Arg Ser
        35                  40                  45
Pro Glu Ala Gly Glu Lys Val Leu Val Asn Gly Gly Leu Thr Pro Pro
    50                  55                  60
Lys Ser Glu Asp Lys Val Ser Glu Asn Gly Gly Leu Arg Phe Pro Arg
65                  70                  75                  80
Asn Thr Glu Arg Pro Pro Glu Thr Gly Pro Trp Arg Ala Pro Gly Pro
                85                  90                  95
Trp Glu Lys Thr Pro Glu Ser Trp Gly Pro Ala Pro Thr Ile Gly Glu
            100                 105                 110
Pro Ala Pro Glu Thr Ser Leu Glu Arg Ala Pro Ala Pro Ser Ala Val
        115                 120                 125
Val Ser Ser Arg Asn Gly Gly Glu Thr Ala Pro Gly Pro Leu Gly Pro
    130                 135                 140
```

```
Ala Pro Lys Asn Gly Thr Leu Glu Pro Gly Thr Glu Arg Arg Ala Pro
145                 150                 155                 160
Glu Thr Gly Gly Ala Pro Arg Ala Pro Gly Ala Gly Arg Leu Asp Leu
                165                 170                 175
Gly Ser Gly Gly Arg Ala Pro Val Gly Thr Gly Thr Ala Pro Gly Gly
            180                 185                 190
Gly Pro Gly Ser Gly Val Asp Ala Lys Ala Gly Trp Val Asp Asn Thr
        195                 200                 205
Arg Pro Gln Pro Pro Pro Pro Pro Leu Pro Pro Pro Pro Glu Ala Gln
    210                 215                 220
Pro Arg Arg Leu Glu Pro Ala Pro Pro Arg Ala Arg Pro Glu Val Ala
225                 230                 235                 240
Pro Glu Gly Glu Pro Gly Ala Pro Asp Ser Arg Ala Gly Gly Asp Thr
                245                 250                 255
Ala Leu Ser Gly Asp Gly Asp Pro Pro Lys Pro Glu Arg Lys Gly Pro
            260                 265                 270
Glu Met Pro Arg Leu Phe Leu Asp Leu Gly Pro Pro Gln Gly Asn Ser
        275                 280                 285
Glu Gln Ile Lys Ala Arg Leu Ser Arg Leu Ser Leu Ala Leu Pro Pro
    290                 295                 300
Leu Thr Leu Thr Pro Phe Pro Gly Pro Gly Pro Arg Arg Pro Pro Trp
305                 310                 315                 320
Glu Gly Ala Asp Ala Gly Ala Ala Gly Gly Glu Ala Gly Gly Ala Gly
                325                 330                 335
Ala Pro Gly Pro Ala Glu Glu Asp Gly Glu Asp Glu Asp Glu Asp Glu
            340                 345                 350
Glu Glu Asp Glu Glu Ala Ala Ala Pro Gly Ala Ala Ala Gly Pro Arg
        355                 360                 365
Gly Pro Gly Arg Ala Arg Ala Ala Pro Val Pro Val Val Val Ser Ser
    370                 375                 380
Ala Asp Ala Asp Ala Ala Arg Pro Leu Arg Gly Leu Leu Lys Ser Pro
385                 390                 395                 400
Arg Gly Ala Asp Glu Pro Glu Asp Ser Glu Leu Glu Arg Lys Arg Lys
                405                 410                 415
Met Val Ser Phe His Gly Asp Val Thr Val Tyr Leu Phe Asp Gln Glu
            420                 425                 430
Thr Pro Thr Asn Glu Leu Ser Val Gln Ala Pro Pro Glu Gly Asp Thr
        435                 440                 445
Asp Pro Ser Thr Pro Pro Ala Pro Pro Thr Pro Pro His Pro Ala Thr
    450                 455                 460
Pro Gly Asp Gly Phe Pro Ser Asn Asp Ser Gly Phe Gly Gly Ser Phe
465                 470                 475                 480
Glu Trp Ala Glu Asp Phe Pro Leu Leu Pro Pro Pro Gly Pro Pro Leu
                485                 490                 495
Cys Phe Ser Arg Phe Ser Val Ser Pro Ala Leu Glu Thr Pro Gly Pro
            500                 505                 510
Pro Ala Arg Ala Pro Asp Ala Arg Pro Ala Gly Pro Val Glu Asn
        515                 520                 525
```

<210> 217
<211> 466
<212> DNA
<213> Homo sapien

<400> 217

```
gaatggtgcc tgtcctgctg tctctgctgc tgcttctggg tcctgctgtc ccccaggaga      60
accaagatgg tcgttactct ctgacctata tctacactgg gctgtccaag catgttgaag     120
acgtccccgc gtttcaggcc cttggctcac tcaatgacct ccagttcttt agatacaaca     180
```

gtaaagacag gaagtctcag cccatgggac tctggagaca ggtggaagga atggaggatt 240
ggaagcagga cagccaactt cagaaggcca gggaggacat ctttatggag accctgaaag 300
acatcgtgga gtattacaac gacagtaacg ggtctcacgt attgcaggga aggtttggtt 360
gtgagatcga gaataacaga agcagcggag cattctggaa atattactat gatggaaagg 420
actacattga attcaacaaa gaaatcccag cctgggtccc cttcga 466

<210> 218
<211> 381
<212> DNA
<213> Homo sapien

<400> 218
gagtttcctt cgcaagttca tgtggggtac cttcccaggc tgcctggctg accagctggt 60
tttaaagcgc cggggtaacc agttggagat ctgtgccgtg gtcctgaggc agttgtctcc 120
acacaagtac tacttcctcg tgggctacag tgaaactttg ctgtcctact tttacaaatg 180
tcctgtgcga ctccacctcc aaactgtgcc ctcaaaggtt gtgtataagt acctctagaa 240
caatcccctt ttttccatca agctgtagcc tgcagagaat ggaaacgtgg gaaaggaatg 300
gtatgtgggg gaaatgcatc ccctcagagg actgaggcat agtctctcat ctgctattga 360
ataaagacct tctatcttgt a 381

<210> 219
<211> 1293
<212> DNA
<213> Homo sapien

<400> 219
gaggggaggc gcatggcggg gatggcgctg gcgcgggcct ggaagcagat gtcctggttc 60
tactaccagt acctgctggt cacggcgctc tacatgctgg agccctggga gcggacggtg 120
ttcaattcca tgctggtttc cattgtgggg atggcactat acacaggata cgtcttcatg 180
ccccagcaca tcatggcgat attgcactac tttgaaatcg tacaatgacc aagatgcgac 240
caggatcaga ggttccttgg ggaagaccca ccctacgaag ttggaatgag accatcagat 300
gtgataagaa actcttctag atgtcaacat aaccaacctt ataaagacta aaattcatga 360
gtagaacagg aaaatcatcc tgactcatgt gttgtgttct ttatttttaa ttttcaaaga 420
ggctcttgta tagcagtttt tgtctatttt aacattgtag tcatttgtac tttgatatca 480
gtattttctt aacctttgtg actgtttcaa tattaccccc gtgaaagctt ttcttaatgt 540
aactttgagt acattttaat tgccttctat ttttaaaact caaaatcatt agttgggctt 600
tactgttctt gctattgtat ggcatataca tctgcctgga tatatttcta ctcttgacca 660
aagttttgta aagaacaata taagatttcg ggtaggggta tggggaggga agatatttta 720
ttgagaacta cttaacaaaa gatttatctg taagcttgaa ctcaggagta cagttttagc 780
tatctagact ctaacagctt ttgctttaaa attattaaag tgtttcttaa tgaaaaagaa 840
aagatcttgc taaagttaaa ataaggaaca tttcaccttt taaatattta attcttatgt 900
ggacttattt ccagaaaact ttggtgataa ttcttgagac aaaaggtggt taagtagcat 960
tattatgtaa tgcttatata ccatagagtt tttaatagaa gagaaatcca tttcctccga 1020
gggtcactat taacaatgta cttccttaaa tttagtttaa tgattgtaat gggtgctgca 1080
tttgcacatt gcattaagtt atgatgagac gaattgttgt taaaaattat agcaaaaaga 1140
aatgtaaact tggttaaaat cctttcactc tttgtattgt ttttttaag gtttttattc 1200
cttaaatgta aaatgactac ctaatttttt gatgtaaata cattaaattc aaagagaaaa 1260
aaaatcaaaa aaaaaaaaaa aaaaaaactc gag 1293

<210> 220
<211> 983
<212> DNA
<213> Homo sapien

<400> 220
caggttattc tgatcctgcc gcctgtcttc cctgtaagag tggagcctcg aggtgtacct 60
taaagtgacc ggaatgttag agatgcaatt tgcagagctg gggcaaggaa gggctccttg 120
tcactgtagt tactttcctt gcagtggcca aatgcccaat aagaaggaat acatgaccac 180

tgctgtgggg agtcagcagg tgcgtgatgc agctggccac actccatcca cggccatgac 240
ataaaacaga caagaagtaa ggctggactg taacacctca aggcctgctc cagtgaccca 300
ctttcttcag agaggctcta ccacacacac aaccaccttc caaatttaca ctcagatcac 360
tacaccatgt ctcccaagtt aaaacatgta tccacctaga ctttaaatgt gctttgtaac 420
tgttgatggc actgtacaga gggccaaagt atttcccatc agatagcatt tttctgaacc 480
catgcctctt gggacgagat cacaggactt gacccatcat caaataggac caggtgacct 540
acagagacat cacaatgatg gcttcctaca gtcaagtcca tttccaataa tgctctcatc 600
taagagaacc catgaacctt atttgaatcc tggttcaaac aaaaacctta aattatttat 660
gagacaatta taaacttgat agattttgat gtgtgaaggt atttatgaat atttttagtc 720
agtgatggta tactgttaag gaaaaggttc atattttagg gacaaaggct gaaacattta 780
tggacagagt gatatgatat ctgggatttg ttttaggatg aagtgggagg gaggaaatga 840
atggaaatag tgttgaaaca gtattggcca cgagtcagct attgtgtgct aagacgctcc 900
tcacaccagt ctactctgta tgtgtttgaa tatctctgta ataaacttaa caaggaaaaa 960
aaaaaaaaaa aaaaaaactc gag 983

<210> 221
<211> 373
<212> DNA
<213> Homo sapien

<400> 221
cattttatgg gttaattttt tattaaatag caataagata cttttataac tcaataaaat 60
tattcaatga tacattcgga aaataaatgt ataaaatatg aaaaagtact aaaaagcatt 120
tttcagtact tttaggtaag attaatccaa ctaaacacta gcatatgtta tacagtaata 180
ataaggggaa aatacaataa tgttgagaaa gcaaactcaa agcatagatc aatgaaaaaa 240
ttgagaaatg gacataaatg atttagtatt tttaaagaga gtgaaaaatc attattttat 300
gcttttgtgt agcgttagat gaattaaata acatatgcac atatagcttt gcgatacaaa 360
tttccagacc ata 373

<210> 222
<211> 544
<212> DNA
<213> Homo sapien

<400> 222
cagagatgct gctgctacaa aggatcggtg taagcagtta acccaggaaa tgatgacaga 60
gaaagaaaga agcaatgtgg ttataacaag gatgaaagat cgaattggaa cattagaaaa 120
ggaacataat gtatttcaaa acaaaataca tgtcagttat caagagactc aacagatgca 180
gatgaagttt cagcaagttc gtgagcagat ggaggcagag atagctcact tgaagcagga 240
aaatggtata ctgagagatg cagtcagcaa cactacaaat caactggaaa gcaagcagtc 300
tgcagaacta aataaactac gccaggatta tgctaggttg gtgaatgagc tgactgagaa 360
aacaggaaag ctacagcaag aggaagtcca aaagaagaat gctgagcaag cagctactca 420
gttgaaggtt caactacaag aagctgagag aaggtgggaa gaagttcaga gctacatcag 480
gaagagaaca gcggaacatg aggcagcaca gctagattta cagagtaaat ttgtggccaa 540
agaa 544

<210> 223
<211> 316
<212> DNA
<213> Homo sapien

<400> 223
gaggcaaggg atatgcttta gtgcctatta tagttaattc ttcaactcca aagtctaaaa 60
cagttgaatc tgctgaagga aaatctgaag aagtaaatga aacattagtt atacccactg 120
aggaagcaga aatggaagaa agtggacgaa gtgcaactcc tgttaactgt gaacagcctg 180
atatcttggt ttcttctaca ccaataaatg aaggacagac tgtgttagac aaggtggctg 240
agcagtgtga acctgctgaa agtcagccag aagcacttct gagaggaaga tgtttgcaag 300
gtaactctaa cagttg 316

<210> 224
<211> 1583
<212> DNA
<213> Homo sapien

<400> 224
cagaccacgt ctgccctcgc cgctctagcc ctgcgcccca gcccggccgc ggcacctccg 60
cctcgccgcc gctaggtcgg ccggctccgc ccggctgccg cctaggatga atatcatgga 120
cttcaacgtg aagaagctgg cggccgacgc aggcaccttc ctcagtcgcg ccgtgcagtt 180
cacagaagaa aagcttggcc aggctgagaa gacagaattg gatgctcact tagagaacct 240
ccttagcaaa gctgaatgta ccaaaatatg gacagaaaaa ataatgaaac aaactgaagt 300
gttattgcag ccaaatccaa atgccaggat agaagaattt gtttatgaga aactggatag 360
aaaagctcca agtcgtataa acaacccaga acttttggga caatatatga ttgatgcagg 420
gactgagttt ggcccaggaa cagcttatgg taatgccctt attaaatgtg gagaaaccca 480
aaaaagaatt ggaacagcag acagagaact gattcaaacg tcagccttaa attttcttac 540
tcctttaaga aactttatag aaggagatta caaaacaatt gctaaagaaa ggaaactatt 600
gcaaaataag agactggatt tggatgctgc aaaaacgaga ctaaaaaagg caaaagctgc 660
agaaactaga aattcatctg aacaggaatt aagaataact caaagtgaat ttgatcgtca 720
agcagagatt accagacttc tgctagaggg aatcagcagt acacatgccc atcaccttcg 780
ctgtctgaat gactttgtag aagcccagat gacttactat gcacagtgtt accagtatat 840
gttggacctc cagaaacaac tgggaagttt tccatccaat tatcttagta acaacaatca 900
gacttctgtg acacctgtac catcagtttt accaaatgcg attggttctt ctgccatggc 960
ttcaacaagt ggcctagtaa tcacctctcc ttccaacctc agtgacctta aggagtgtag 1020
tggcagcaga aaggccaggg ttctctatga ttatgatgca gcaaacagta ctgaattatc 1080
acttctggca gatgaggtga tcactgtgtt cagtgttgtt ggaatggatt cagactggct 1140
aatgggggaa aggggaaacc agaagggcaa ggtgccaatt acctacttag aactgctcaa 1200
ttaagtaggt ggactatgga aaggttgccc atcatgactt tgtatttata tacaattaac 1260
tctaaataaa gcaggttaag tatcttccat gttaatgtgt taagagactg aaaataccag 1320
ccatcagaaa ctggcctttt tgccaataaa gttgcatggt aaatatttca ttacagaatt 1380
tatgttagag ctttcatgcc aagaatgttt tcttacaaaa ttctcttttt attgaggttt 1440
cactaataag cagcttctac ttttgagcct caacttaaag cagaactgtt ttttactgga 1500
tttttcatta acagcaagct tttttttttа tgtaaaataa atctattgtg aattgaaaaa 1560
aaaaaaaaaa aaaaaaactc gag 1583

<210> 225
<211> 491
<212> DNA
<213> Homo sapien

<400> 225
gaacaacatc atcttgaatc actagataga ctcttgacgg aaagcaaagg ggaaatgaaa 60
aaggaaaata tgaagaaaga tgaagcttta aaagcattac agaaccaagt atctgaagaa 120
acaatcaagg ttaggcaact agattcagca ttggaaattt gtaaggaaga acttgtcttg 180
catttgaatc aattggaagg aaataaggaa aagtttgaaa aacagttaaa gaagaaatct 240
gaagaggtat attgtttaca gaaagagcta aagataaaaa atcacagtct tcaagagact 300
tctgagcaaa acgttattct acagcatact cttcagcaac agcagcaaat gttacaacaa 360
gagacaatta gaaatggaga gctagaagat actcaaacta aacttgaaaa acaggtgtca 420
aaactggaac aagaacttca aaaacaaagg gaaagttcag ctgaaaagtt gagaaaaatg 480
gaggagaaat g 491

<210> 226
<211> 483
<212> DNA
<213> Homo sapien

<400> 226
cagccgcacg ccgcggagca ggggctcgga ggtcccggga ttacggtgct cgagcacgct 60

ggtgggaaag gacccgggac ttgaacagtg ttgtgcggcg ccatgcaggt ctccagcctc 120
aatgaggtga agatttacag cctcagctgc ggcaagtccc ttcctgagtg gctttctgat 180
aggaagaaga gagcgctaca gaagaaagat gtagatgtcc gtaggagaat tgaacttatt 240
caggactttg aaatgcctac tgtgtgtacc actattaagg tgtcaaaaga tggacagtac 300
attttagcaa ctggaacata taaacctcgg gttcgatgtt atgacaccta tcaattatcc 360
ttgaagtttg aaaggtgttt agattcagaa gttgtcacct ttgaaatttt gtctgatgac 420
tactcaaaga ttgtcttctt acataatgat agatacattg aatttcattc gcaatcaggt 480
ttt 483

<210> 227
<211> 486
<212> DNA
<213> Homo sapien

<400> 227
gagcctcgct aagctccgac tctgggcggc accgggcgtc ccacgatgcc gaagaacaag 60
aagcggaaca ctccccaccg cggtagcagt gctggcggcg gcgggtcagg agcagccgca 120
gcgacggcgg cgacagcagg tggccagcat cgaaatgttc agccttttag tgatgaagat 180
gcatcaattg aaacagtgag ccattgcagt ggttatagcg atccttccag ttttgctgaa 240
gatggaccag aagtccttga tgaggaagga actcaagaag acctagagta caagttgaag 300
ggattaattg acctaaccct ggataagagt gcgaagacaa ggcaagcagc tcttgaaggt 360
attaaaaatg cactggcttc aaaaatgctg tatgaattta ttctggaaag gagaatgact 420
ttaactgata gcattgaacg ctgcctgaaa aaaggtaaga gtgatgagca acgtgcagct 480
gcagcg 486

<210> 228
<211> 494
<212> DNA
<213> Homo sapien

<400> 228
gaggccagga ctccgggaat gcgagcaggc cccttattct cccagtggcc tcggtctgtc 60
cccacagcgg cccggtcagg gttgcccgag ccccaaggcg gggggcggca ccggggtgct 120
gaaagggaca gaatgctttg acctccaagc tgttttaaat ctagtagata agccagatcc 180
tgtgttgcca taagcccttg gcccacattt aagtgggaat gcagctagct tggatgtctg 240
aaactttgta agcgccttct gtctgaatcc tgaacacagg caccaagact actgaagaag 300
ctcgtcattc ttgtgcaggg atagccacac aagcaaacat gtttgcaaaa cttgaaagaa 360
agaaaattgc agaaagaaga cttgctgttc ttaagaggcc caggaaggtg ctacttagga 420
atcccaccgg cttgtgaagc aagggaatca agtttgcctt caatggggaa cttgacttca 480
ggaaaatgaa cttt 494

<210> 229
<211> 465
<212> DNA
<213> Homo sapien

<400> 229
gtcagagagc tggtataacc tcctgttgga catgcagaac cgactcaata aggtcatcaa 60
aagcgtgggc aagattgagc actccttctg gagatccttt cacactgagc gaaagacaga 120
accagccaca ggcttcatcg atggtgatct gattgaaagt ttcctagata tcagccgccc 180
taagatgcag gaggttgtgg caaacttgca gtatgatgat ggcagtggta tgaagcggga 240
ggcaactgca gatgacctca tcaaagtcgt ggaggaacta actcggatcc attagccaag 300
gacaggatct cttttcctga ccctcctaaa ggcgttgccc tcctatcctc ccttccttgc 360
ccacccttgg tttctttggc atgggaaggt tttccttaac cacttgccct agagccacca 420
gtgaccttgt gtggaaacag ggtttttttt acttaaaaca gttca 465

<210> 230
<211> 495

<212> DNA
<213> Homo sapien

<400> 230
caggggaaag ggtgtttggc cttgaccagc cactgctgac ctcaatctca gacctacaga 60
tggtgaatat ctccctgcga gtgttgtctc gacccaatgc tcaggagctt cctagcatgt 120
accagcgcct agggctggac tacgaggaac gagtgttgcc gtccattgtc aacgaggtgc 180
tcaagagtgt ggtggccaag ttcaatgcct cacagctgat cacccagcgg gcccaggtat 240
ccctgttgat ccgccgggag ctgacagaaa gggccaaagg acttcagcct catcctggat 300
gatgtggcca tcacagactt gagctttagc cgagaagtac acaagctgcc tgtaagaaac 360
ccaaccaagt ggggtgaatt ccaaaaaccc gtgggggtga agggcttctt aagaatgcaa 420
ggaaggagga aaagaattcc atgggggggg ggttccttaa cccaggaaca ggggtttccc 480
ttgaattttt ttcca 495

<210> 231
<211> 498
<212> DNA
<213> Homo sapien

<400> 231
ggcagcttct gagaccaggg ttgctccgtc cgtgctccgc ctcgccatga cttcctacag 60
ctatcgccag tcgtcggcca cgtcgtcctt cggaggcctg ggcggcggct ccgtgcgttt 120
tgggccgggg gtcgcttttc gcgcgcccag cattcacggg ggctccggcg gccgcggcgt 180
atccgtgtcc tccgcccgct ttgtgtcctc gtcctcctcg gggggctacg gcggcggcta 240
cggcggcgtc ctgaccgcgt ccgacgggct gctggcgggc aacgagaagc taaccatgca 300
gaacctcaac gaccgcctgc ctcctacctg gacaaagtgc gcgccctgga agcgggcaac 360
ggcgaactta gaggtgaaag aatcccgcga actggtacca aaaacaaggg gcctggggcc 420
ttccgcgact tacagccaac ttactacacc gaacattcaa gaacttgcgg gaacaaaaat 480
ttttggtgcc acccattt 498

<210> 232
<211> 465
<212> DNA
<213> Homo sapien

<400> 232
caggccggcc gagtaggaaa gctggaggcg cgggtgggga acatgtctga gtcggagctc 60
ggcaggaagt gggaccggtg tctggcggat gcggtcgtga agataggtac tggttttgga 120
ttaggaattg ttttctcact taccttcttt aaaagaagaa tgtggccatt agccttcggt 180
tctggcatgg gattaggaat ggcttattcc aactgtcagc atgatttcca ggctccatat 240
cttctacatg gaaaatatgt caaagagcag gagcagtgac ttcacctgag aacatcccag 300
cgggaggaca agagaaaatc atgtttattc ctcaggaata cttgaagtgc cctggagtaa 360
actgccattc ttctgtaaca atggtatcag taatgcttta aactccagca cctggttatg 420
catttgaaac ccaagtctgg ttcttggttt ggattttctc tctgg 465

<210> 233
<211> 366
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 90, 97, 242, 244
<223> n = A,T,C or G

<400> 233
cagtaaaaaa ggttatgttt tattaattgc tggacaaccg tgggaaaaca aataagcaat 60
tgacaccacc aaattcttat tacattcaan ataaaanatt tattcacacc acaaaaagat 120

aatcacaaca aaatatacac taacttaaaa aacaaaagat tatagtgaca taaaatgtta 180
tattctcttt ttaagtgggt aaaagtattt tgtttgcttc tacataaatt tctattcatg 240
ananaataac aaatattaaa atacagtgat agtttgcatt tcttctatag aatgaacata 300
gacataaccc tgaagctttt agtttacagg gagtttccat gaagccacaa actaaactaa 360
ttatca 366

<210> 234
<211> 379
<212> DNA
<213> Homo sapiens

<400> 234
gagggcagcc ctcctacctg cgcacgtggt gccgccgctg ctgcctcccg ctcgccctga 60
acccagtgcc tgcagccatg gctcccggcc agctcgcctt atttagtgtc tctgacaaaa 120
ccggccttgt ggaatttgca agaaacctga ccgctcttgg tttgaatctg gtcgcttccg 180
gagggactgc aaaagctctc agggatgctg gtctggcagt cacagatgtc tctgagttga 240
cgggatttct gaaatgttgg ggggacgtgt gaaaactttg catcctgcac gatcccatgc 300
tggaatccta gctcctaata ttcagaagat aatgcttgac atgcgccaca cttgattcaa 360
tcttataaca attgttgcc 379

<210> 235
<211> 406
<212> DNA
<213> Homo sapiens

<400> 235
caggctgcac catgtacccc accttcagtt taaaagaaaa aaaaaatccc cttcactcct 60
actgggaggt gggacccctt tcattttcag ttttgctcat ctagggaaaa taaggctttg 120
gtttccagtt taattgtttt tgaccttcta aaatgttttt atgttagcac tgatagttgg 180
cattactgtt gttaagcact gtgttccaga ccgtgtctga cttagtgtaa cctaggagat 240
tttatagttt tattttaatg aaaccctgat tgacgcacag cagtggggag aacagcgtct 300
tttacctgtc accgaagcca ggaagccccg tttgtaagcg tgtgttgtgg tgctttattg 360
tacatcctcc agtggcgttc tttttactct aatgttcttt tggttt 406

<210> 236
<211> 278
<212> DNA
<213> Homo sapiens

<400> 236
gagattagca cctgtgaaca atgcgttctc tgatgacact ctgagcatgg accaacgcct 60
tcttaagcta attctgcaaa atcacatatt gaaagtaaaa gttggcctta gcgacctcta 120
caatggacag atactggaaa ccattggagg caaacaactc cgagtctttg tgtatcggac 180
ggctatctgc atagaaaact catgcatggt gagaggaagc aagcagggaa ggaacggtgc 240
cattcacata ttccgagaga tcatccaacc agcagaat 278

<210> 237
<211> 322
<212> DNA
<213> Homo sapiens

<400> 237
cagggccgtg gcggaggagg agcgctgcac ggtggagcgt cgggccgacc tcacctacgc 60
ggagttcgtg cagcagtacg tgcgcccctg atcgcggagg tcgcgtcctg ttcaccggcc 120
cgtctgcccc gaccgcccaa ggccgccttc ccctgacctc gcgcgcacgc gtggggctgg 180
ggcggcgagg ctggcggtcc ggcctggccg cgactctgcc cttctttcca gaggttccgg 240
gccctgtgct cccgcgacag gttgctggct tcgtttgggg acagagtggt ccggtgagca 300
ccgccaacac ctactcctac ct 322

<210> 238
<211> 613
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 399
<223> n = A,T,C or G

<400> 238
gaattcggca ccagccttct tggatcagga ccagtctcca ccccgtttct acagtggaga 60
tcagcctcct tcttatcttg gtgcaagtgt ggataaactc catcaccctt tagaatttgc 120
agacaaatct cccacacctc ctaatttacc tagcgataaa atctaccctc cttctgggtc 180
ccccgaagag aataccagca cagccaccat gacttacatg acaactactc cagcaacagc 240
ccaaatgagc accaaggaag ccagctggga tgtggctgaa caacccacca ctgctgattt 300
tgctgctgcc acacttcagc gcacgcacag aactaatcgt ccccttcccc ctccgccttc 360
ccagagatct gcagagcagc caccagttgt ggggcaggna caagcagcaa ccaatatagg 420
attaaataat tcccacaagg ttcaaggagt agttccagtt ccagagaggc cacctgaacc 480
tcgagccatg gatgaccctg cgtctgcctt catcagtgac agtggtgctg ctgctgctca 540
gtgtcccatg gctacagctg tccagccagg cctgcctgag aaagtgcggg acggtgcccg 600
ggtcccgctg ctg 613

<210> 239
<211> 613
<212> DNA
<213> Homo sapiens

<400> 239
gaattcggca ccaggggaca ctggtgctga gctggatgat gatcagcact ggtctgacag 60
cccgtcggat gctgacagag agctgcgttt gccgtgccca gctgaggggg aagcagagct 120
ggagctgagg gtgtcggaag atgaggagaa gctgcccgcc tcaccgaagc accaagagag 180
aggtccctcc caagccacca gccccatccg gtctccccag gaatcagctc ttctgttcat 240
tccagtccac agcccctcaa cagaggggcc ccaactccca cctgtccctg ccgccaccca 300
ggagaaatca cctgaggagc gccttttccc tgagcctttg ctccccaaag agaagcccaa 360
agctgatgcc ccctcggatc tgaaagctgt gcactctccc atccgatcac agccagtgac 420
cctgccagaa gctaggactc ctgtctcacc agggagcccg cagccccagc cacccgtggc 480
ggcctccacg cccccaccca gcgaggtctc cagagccttc tctctcctgt gcaaaatggc 540
aactcttaag gaaaaactca ttgcaccagt tgcggaagaa gaggcaacag ttccaaacaa 600
taagatcact gta 613

<210> 240
<211> 585
<212> DNA
<213> Homo sapiens

<400> 240
gaattcggca cgaggtgaga tctacgatga actttaagat tggaggtgtg acagaacgca 60
tgccaacccc agttattaaa gcttttggca tcttgaagcg agcggccgct gaagtaaacc 120
aggattatgg tcttgatcca aagattgcta atgcaataat gaaggcagca gatgaggtag 180
ctgaaggtaa attaaatgat cattttcctc tcgtggtatg gcagactgga tcaggaactc 240
agacaaatat gaatgtaaat gaagtcatta gcaatagagc aattgaaatg ttaggaggtg 300
aacttggcag caagatacct gtgcatccca acgatcatgt taataaaagc cagagctcaa 360
atgatacttt tcccacagca atgcacattg ctgctgcaat agaagttcat gaagtactgt 420
taccaggact acagaagtta catgatgctc ttgatgcaaa atccaaagag tttgcacaga 480
tcatcaagat tggacgtact catactcagg atgctgttcc acttactctt gggcaggaat 540
ttagtggtta tgttcaacaa gtaaaatatg caatgacaag aataa 585

<210> 241
<211> 566
<212> DNA
<213> Homo sapiens

<400> 241
gaattcggca ccaggcgagc tgcacctcga ggtgaaggcc tcactgatga acgatgactt 60
cgagaagatc aagaactggc agaaggaagc ctttcacaag cagatgatgg gcggcttcaa 120
ggagaccaag gaagctgagg acggctttcg gaaggcacag aagccctggg ccaagaagct 180
gaaagaggta gaagcagcaa agaaagccca ccatgcagcg tgcaaagagg agaagctggc 240
tatctcacga gaagccaaca gcaaggcaga cccatccctc aaccctgaac agctcaagaa 300
attgcaagac aaaatagaaa agtgcaagca agatgttctt aagaccaaag agaagtatga 360
gaagtccctg aaggaactcg accagggcac accccagtac atggagaaca tggagcaggt 420
gtttgagcag tgccagcagt tcgaggagaa acgccttcgc ttcttccggg aggttctgct 480
ggaggttcag aagcacctag acctgtccaa tgtggctggc tacaaagcca tttaccatga 540
cctggagcag agcatcagag cagctg 566

<210> 242
<211> 556
<212> DNA
<213> Homo sapiens

<400> 242
gaattcggca cgagcaaagg tgaagcagga catgcctccg cccgggggct atgggcccat 60
cgactacaaa cggaacttgc cgcgtcgagg actgtcgggc tacagcatgc tggccatagg 120
gattggaacc ctgatctacg ggcactggag cataatgaag tggaaccgtg agcgcaggcg 180
cctacaaatc gaggacttcg aggctcgcat cgcgctgttg ccactgttac aggcagaaac 240
cgaccggagg accttgcaga tgcttcggga gaacctggag gaggaggcca tcatcatgaa 300
ggacgtgccc gactggaagg tgggggagtc tgtgttccac acaacccgct gggtgccccc 360
cttgatcggg gagctgtacg ggctgcgcac cacagaggag gctctccatg ccagccacgg 420
cttcatgtgg tacacgtagg ccctgtgccc tccggccacc tggatccctg cccctcccca 480
ctgggacgga ataaatgctc tgcagacctg gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 540
aaaaaaaaaa ctcgag 556

<210> 243
<211> 591
<212> DNA
<213> Homo sapiens

<400> 243
gtctatgttt gcagaaatac agatccaaga caaagacagg atgggcactg ctggaaaagt 60
tattaaatgc aaagcagctg tgctttggga gcagaagcaa cccttctcca ttgaggaaat 120
agaagttgcc ccaccaaaga ctaaagaagt tcgcattaag attttggcca caggaatctg 180
tcgcacagat gaccatgtga taaaaggaac aatggtgtcc aagtttccag tgattgtggg 240
acatgaggca actgggattg tagagagcat tggagaagga gtgactacag tgaaaccagg 300
tgacaaagtc atccctctct ttctgccaca atgtagagaa tgcaatgctt gtcgcaaccc 360
agatggcaac ctttgcatta ggagcgatat tactggtcgt ggagtactgg ctgatggcac 420
caccagattt acatgcaagg gcaaaccagt ccaccacttc atgaacacca gtacatttac 480
cgagtacaca gtggtggatg aatcttctgt tgctaagatt gatgatgcag ctcctcctga 540
gaaagtctgt ttaattggct gtgggttttc cactggatat ggcgctgctg t 591

<210> 244
<211> 594
<212> DNA
<213> Homo sapiens

<400> 244

gaattcggca cgagaacaga gtgaactgag catcagtcag aaaaagtcta tgtttgcaga 60
aatacagatc caagacaaag acaggatggg cactgctgga aaagttatta aatgcaaagc 120
agctgtgctt tgggagcaga agcaaccctt ctccattgag gaaatagaag ttgccccacc 180
aaagactaaa gaagttcgca ttaagatttt ggccacagga atctgtcgca cagatgacca 240
tgtgataaaa ggaacaatgg tgtccaagtt tccagtgatt gtgggacatg aggcaactgg 300
gattgtagag agcattggag aaggagtgac tacagtgaaa ccaggtgaca aagtcatccc 360
tctctttctg ccacaatgta gagaatgcaa tgcttgtcgc aacccagatg gcaacctttg 420
cattaggagc gatattactg gtcgtggagt actggctgat ggcaccacca gatttacatg 480
caagggcaaa ccagtccacc acttcatgaa caccagtaca tttaccgagt acacagtggt 540
ggatgaatct tctgttgcta agattgatga tgcagctcct cctgagaaag tctg 594

<210> 245
<211> 615
<212> DNA
<213> Homo sapiens

<220>
<221> misc_feature
<222> 105
<223> n = A,T,C or G

<400> 245
gtccctttcc tctgctgccg ctcggtcacg cttgtgcccg aaggaggaaa cagtgacaga 60
cctggagact gcagttctct atccttccac agctctttca ccatnctgga tcacttcctt 120
tgaatgcaga agcttgctgg ccaaaagatg tgggaattgt tgcccttgag atctattttc 180
cttctcaata tgttgatcaa gcagagttgg aaaaatatga tggtgtagat gctggaaagt 240
ataccattgg cttgggccag gccaagatgg gcttctgcac agatagagaa gatattaact 300
ctctttgcat gactgtggtt cagaatctta tggagagaaa taacctttcc tatgattgca 360
ttgggcggct ggaagttgga acagagacaa tcatcgacaa atcaaagtct gtgaagacta 420
atttgatgca gctgtttgaa gagtctggga atacagatat agaaggaatc gacacaacta 480
atgcatgcta tggaggcaca gctgctgtct tcaatgcttg ttaactggat tgagtccagc 540
tcttgggatg gacggtatgc cctggtaagt tgcaggagat attgctgtat atgccacagg 600
aaatgctaga cctac 615

<210> 246
<211> 546
<212> DNA
<213> Homo sapiens

<400> 246
gaattcggca ccaggctgcc tcccgctcgc cctgaaccca gtgcctgcag ccatggctcc 60
cggccagctc gccttattta gtgtctctgc aaaaccggcc ttgtgaattt gcaagaaacc 120
tgaccgctct tggtttgaat ctggtcgctt ccggagggac tgcaaaagct ctcagggatg 180
ctggtctggc agtcagagat gtctctgagt tgacgggatt tcctgaaatg ttgggggggac 240
gtgtgaaaac tttgcatcct gcagtccatg ctggaatcct agctcgtaat attccagaag 300
ataatgctga catggccaga cttgatttca atcttataag agttgttgcc tgcaatctct 360
atcctttgt aaagacagtg gcttctccag gtgtaactgt tgaggaggct gtggagcaaa 420
ttgacattgg tggagtaacc ttactgagag ctgcagccaa aaaccacgct cgagtgacag 480
tggtgtgtga accagaggac tatgtgggtg ggtgtccacg gagatgcaga gctccgagag 540
taagga 546

<210> 247
<211> 564
<212> DNA
<213> Homo sapiens

<400> 247
gaattcggca ccagagatca cgtgcagtga gatgcagcaa aaagttgaac ttctgagata 60

tgaatctgaa aagcttcaac aggaaaattc tattttgaga aatgaaatta ctactttaaa 120
tgaagaagat agcatttcta acctgaaatt agggacatta aatggatctc aggaagaaat 180
gtggcaaaaa acggaaactg taaaacaaga aaatgctgca gttcagaaga tggttgaaaa 240
tttaaagaaa cagatttcag aattaaaaat caaaaaccaa caattggatt tggaaaatac 300
agaacttagc caaaagaact ctcaaaacca ggaaaaactg caagaactta atcaacgtct 360
aacagaaatg ctatgccaga aggaaaaaga gccaggaaac agtgcattgg aggaacggga 420
acaagagaag tttaatctga aagaagaact ggaacgttgt aaagtgcagt cctccacttt 480
agtgtcttct ctggaggcgg agctctctga agttaaaata cagacccata ttgtgcaaca 540
ggaaaaccac cttctcaaag atga 564

<210> 248
<211> 434
<212> DNA
<213> Homo sapiens

<400> 248
gttcttgttt gtggatcgct gtgatcgtca cttgacaatg cagatcttcg tgaagactct 60
gactggtaag accatcaccc tcgaggttga gcccagtgac accatcgaga atgtcaaggc 120
aaagatccaa gataaggaag gcatccctcc tgaccagcag aggctgatct ttgctggaaa 180
acagctggaa gatgggcgca ccctgtctga ctacaacatc cagaaagagt ccaccctgca 240
cctggtgctc cgtctcagag gtgggatgca aatcttcgtg aagacactca ctggcaagac 300
catcaccctt gaggtggagc ccagtgacac catcgagaac gtcaaagcaa agatccagga 360
caaggaaggc attcctcctg accagcagag gttgatcttt gccggaaagc cagcctggga 420
agatggggcc gcca 434

<210> 249
<211> 416
<212> DNA
<213> Homo sapiens

<400> 249
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cggacaggac ccgcacagca agcacctgta cacggccgac atgttcacgc acgggatcca 120
gagcgccgcg cacttcgtca tgttcttcgc gccctggtgt ggacactgcc agcggctgca 180
gccgacttgg aatgacctgg gagacaaata caacagcatg gaagatgcca aagtctatgt 240
ggctaaagtg gactgcacgg cccactccga cgtgtgctcc gcccaggggg tgcgaggata 300
ccccacctta aagcttttca agccaggcca agaagctgtg aagtaccagg gtcctcggga 360
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<210> 250
<211> 504
<212> DNA
<213> Homo sapiens

<400> 250
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attgtgatcc gtcccaggca gtggattagg aggccagaag gagatccctt ccacggtgct 120
aggctgagat ggatcctctc agggcccaac agctggctgc ggagctggag gtggagatga 180
tggccgatat gtacaacaga atgaccagtg cctgccaccg gaagtgtgtg cctcctcact 240
acaaggaagc agagctctcc aagggcgagt ctgtgtgcct ggaccgatgt gtctctaagt 300
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agctgatgaa gagggtgcag cagagctctg ggcctgcatg aggtccctgt cagtatacac 420
cctggggtgt accccacccc ttcccacttt aataaacgtg ctccctgttg ggtgtcatct 480
gtgaagactg ccaggcctag ctct 504

<210> 251
<211> 607
<212> DNA

<213> Homo sapiens

<400> 251
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caatgatgtg gaaaagatgg ccgcacacat gcggatggtt cacattgatg aagagatggg 180
acctaaaaca gattctactt tgagttttga tttgacattg cagcagggta gtcacactaa 240
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tcacttacga gagaggcacc aagttattca gacggttcat ccagttgaga aaaagctcac 540
ctacaaatgt atccattgcc ttggtgtgta taccagcaac atgaccgcct caactatcac 600
tctgcat 607

<210> 252
<211> 618
<212> DNA
<213> Homo sapiens

<400> 252
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cgctgccact ggggtccctg gccccaccga catggcggcg gtgttgagca agtcctggag 120
cgcacggagc tgaacaagct gcccaagtct gtccagaaca aacttgaaaa gttccttgct 180
gatcagcaat ccgagatcga tggcctgaag gggcggcatg agaaatttaa ggtggagagc 240
gaacaacagt attttgaaat agaaaagagg ttgtcccaca gtcaggagag acttgtgaat 300
gaaacccgag agtgtcaaag cttgcggctt gagctagaga aactcaacaa tcaactgaag 360
gcactaactg agaaaaacaa agaacttgaa attgctcagg atcgcaatat tgccattcag 420
agccaattta caagaacaaa ggaagaatta gaagctgaga aaagagactt aattagaacc 480
aatgagagac tatctcaaga acttgaatac ttaacagagg atgttaaacg tctgaatgaa 540
aaacttaaag aaagcaatac aacaaagggt gaacttcagt taaaattgga tgaacttcaa 600
gcttctgatg tttctgtt 618

<210> 253
<211> 1201
<212> DNA
<213> Homo sapiens

<400> 253
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tgtgagtttg gcatgatttg gtcccctggg attctgcctt agcaagaaag aagttggaaa 120
tacttcctgg aagaaaacta aaacaataca aaagccacag cttattgatt gcatgtcagc 180
ccccttacaa atatggacac atttcctagc ctatttccac ctggaggaga tagtaggctg 240
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aaacataatt atcaggctct gaaaattgaa cacaaaaggt tgcaggaaga atatgtaaaa 360
tcacaaaatg aacttaaacg tgtattaatt gaaaagcaag caagccagga aaaattccaa 420
ctgctccttg aagacttaag gggagaatta gtagagaaag ctagagacat agaaaaaatg 480
aaactgcagg tactaacacc acaaaaattg gaattggtaa aagcccaact acaacaagaa 540
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cgactggaga aggacaaaga ggagctacat aaccagctgc ttagtgttga tcccacgaga 780
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agcacactgg ccagtgaagt gaaagagctt aaacatgcaa acaaactaga aataactgac 1140

atcaaactgg aggcagcaag agctaagagt gagctcgaaa gagaaaggaa taagatccaa 1200
a 1201

<210> 254
<211> 560
<212> DNA
<213> Homo sapiens

<400> 254
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accaaaggcc gtgggaaaac ccctctccag ctccagggga ttggtcagga ccacccacta 180
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tctttttcgg gggactgggg gactcctccc aagatcacat tttagcatct ttctctccta 360
ctccatttag aaaaataagt aacaggtgaa atgtggtctc agtgttaacg ggataattct 420
gctaccggct cctccctgat gattctgaaa tacactactg aacgagctct ggctggtcct 480
ttctatcctg gatgtggttc ttctgtgtag caattccttg atgtccagtt tggaaagatg 540
tactcttctc aacaagaaaa 560

<210> 255
<211> 612
<212> DNA
<213> Homo sapiens

<400> 255
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ctcaaagcca tctggcacgc cttcaccgac tcgaccagga ccacagggca aggtctccaa 120
gtcccagctc aaggtccttt cccataacct gtgcacggtg ctgaaggttc ctcatgaccc 180
agttgccctt gaagagcact tcagggatga tgatgagggt ccagtgtcca accagggcta 240
catgccttat ttaaacaggt tcattttgga aaaggtccaa gacaactttg acaagattga 300
attcaatagg atgtgttgga ccctctgtgt caaaaaaaaa cctcacaaag aatcccctgc 360
tcattacaga agaagatgca tttaaaatat gggttatttt caacttttta tctgaggaca 420
agtatccatt aattattgtg tcagaagaga ttgaatacct gcttaagaag cttacagaag 480
ctatgggagg aggttggcag caagaacaat ttgaacatta taaaatcaac tttgatgaca 540
gtaaaaatgg cctttctgca tgggaactta ttgagcttat tggaaatgga cagtttagca 600
aaggcatgga cc 612

<210> 256
<211> 1132
<212> DNA
<213> Homo sapiens

<400> 256
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ccaaggcccc gccgtccagc ttctaagtgc cagatgatgg aggagcgtgc caacctgatg 120
cacatgatga aactcagcat caaggtgttg ctccagtcgg ctctgagcct gggccgcagc 180
ctggatgcgg accatgcccc cttgcagcag ttctttgtag tgatggagca ctgcctcaaa 240
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gagctggtgg agaaactttg tccagaagca tcagatatag cgactagtgt cagaaatctt 360
ccagaattaa agacagctgt gggaagaggc cgagcgtggc tttatcttgc actcatgcaa 420
aagaaactgg cagattatct gaaagtgctt atagacaata aacatctctt aagcgagttc 480
tatgagcctg aggctttaat gatggaggaa gaagggatgg tgattgttgg tctgctggtg 540
ggactcaatg ttctcgatgc caatctctgc ttgaaaggag aagacttgga ttctcaggtt 600
ggagtaatag atttttccct ctaccttaag gatgtgcagg atcttgatgg tggcaaggag 660
catgaaagaa ttactgatgt ccttgatcaa aaaaattatg tggaagaact taaccggcac 720
ttgagctgca cagttgggga tcttcaaacc aagatagatg gcttggaaaa gactaactca 780
aagcttcaag aagagctttc agctgcaaca gaccgaattt gctcacttca agaagaacag 840